Antibiotics for acute otitis media in children (Review)

Venekamp RP, Sanders S, Glasziou PP, Del Mar CB, Rovers MM

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[Intervention Review]

Antibiotics for acute otitis media in children

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ABSTRACT

Background

Acute otitis media (AOM) is one of the most common diseases in early infancy and childhood. Antibiotic use for AOM varies from 56% in the Netherlands to 95% in the USA, Canada and Australia.

Objectives

To assess the effects of antibiotics for children with AOM.

Search methods

We searched CENTRAL (2012, Issue 10), MEDLINE (1966 to October week 4, 2012), OLDMEDLINE (1958 to 1965), EMBASE (January 1990 to November 2012), Current Contents (1966 to November 2012), CINAHL (2008 to November 2012) and LILACS (2008 to November 2012).

Selection criteria

Randomised controlled trials (RCTs) comparing 1) antimicrobial drugs with placebo and 2) immediate antibiotic treatment with expectant observation (including delayed antibiotic prescribing) in children with AOM.

Data collection and analysis

Two review authors independently assessed trial quality and extracted data.

Main results

For the review of antibiotics against placebo, 12 RCTs (3317 children and 3854 AOM episodes) from high-income countries were eligible. However, one trial did not report patient-relevant outcomes, leaving 11 trials with generally low risk of bias. Pain was not reduced by antibiotics at 24 hours (risk ratio (RR) 0.89; 95% confidence interval (CI) 0.78 to 1.01) but almost a third fewer had residual pain at two to three days (RR 0.70; 95% CI 0.57 to 0.86; number needed to treat for an additional beneficial outcome (NNTB) 20) and fewer had pain at four to seven days (RR 0.79; 95% CI 0.66 to 0.95; NNTB 20). When compared with placebo, antibiotics did not alter the number of abnormal tympanometry findings at either four to six weeks (RR 0.92; 95% CI 0.83 to 1.01) or at three months

(RR 0.97; 95% CI 0.76 to 1.24), or the number of AOM recurrences (RR 0.93; 95% CI 0.78 to 1.10). However, antibiotic treatment did lead to a statistically significant reduction of tympanic membrane perforations (RR 0.37; 95% CI 0.18 to 0.76; NNTB 33) and halved contralateral AOM episodes (RR 0.49; 95% CI 0.25 to 0.95; NNTB 11) as compared with placebo. Severe complications were rare and did not differ between children treated with antibiotics and those treated with placebo. Adverse events (such as vomiting, diarrhoea or rash) occurred more often in children taking antibiotics (RR 1.34; 95% CI 1.16 to 1.55; number needed to treat for an additional harmful outcome (NNTH) 14). Funnel plots do not suggest publication bias. Individual patient data meta-analysis of a subset of included trials found antibiotics to be most beneficial in children aged less than two with bilateral AOM, or with both AOM and otorrhoea.

For the review of immediate antibiotics against expectant observation, five trials (1149 children) were eligible. Four trials (1007 children) reported outcome data that could be used for this review. From these trials, data from 959 children could be extracted for the meta-analysis on pain at days three to seven. No difference in pain was detectable at three to seven days (RR 0.75; 95% CI 0.50 to 1.12). No serious complications occurred in either the antibiotic group or the expectant observation group. Additionally, no difference in tympanic membrane perforations and AOM recurrence was observed. Immediate antibiotic prescribing was associated with a substantial increased risk of vomiting, diarrhoea or rash as compared with expectant observation (RR 1.71; 95% CI 1.24 to 2.36).

Authors' conclusions

Antibiotic treatment led to a statistically significant reduction of children with AOM experiencing pain at two to seven days compared with placebo but since most children (82%) settle spontaneously, about 20 children must be treated to prevent one suffering from ear pain at two to seven days. Additionally, antibiotic treatment led to a statistically significant reduction of tympanic membrane perforations (NNTB 33) and contralateral AOM episodes (NNTB 11). These benefits must be weighed against the possible harms: for every 14 children treated with antibiotics, one child experienced an adverse event (such as vomiting, diarrhoea or rash) that would not have occurred if antibiotics had been withheld. Antibiotics appear to be most useful in children under two years of age with bilateral AOM, or with both AOM and otorrhoea. For most other children with mild disease, an expectant observational approach seems justified. We have no trials in populations with higher risks of complications.

PLAIN LANGUAGE SUMMARY

Antibiotics for middle-ear infection (acute otitis media) in children

An acute middle-ear infection (acute otitis media (AOM)) is one of the most common childhood infections, causing pain and deafness. By three years of age, most children have had at least one AOM episode. Though AOM usually resolves without treatment, it is often treated with antibiotics. We assessed the effectiveness of antibiotics as compared to placebo in children with AOM. We included 12 trials with 3317 children and 3854 AOM episodes in this systematic review. Eleven trials reported patient-relevant outcome data. We found that antibiotics were not very useful for most children with AOM; antibiotics did not decrease the number of children with pain at 24 hours (when most children were better anyway), only slightly reduced the number of children with pain in the few days following and did not reduce the number of children with hearing loss (that can last several weeks). However, antibiotic treatment did reduce the number of tympanic membrane perforations and contralateral AOM episodes. Antibiotics seem to be most beneficial in children younger than two years of age with infection in both ears and in children with both AOM and discharge from the ear. There was not enough information to know if antibiotics reduced rare complications such as mastoiditis (infection of the bones around the ear).

Some guidelines have recommended a management approach in which certain children are observed and antibiotics taken only if symptoms remain or have worsened after a few days. We therefore also determined the effectiveness of immediate antibiotics as compared to expectant observation in children with AOM. We identified five eligible trials with 1149 children for this review. Four trials (including 1007 children) did report outcome data that could be used. We found no difference between immediate antibiotics and expectant observational approaches in the number of children with pain three to seven days after assessment.

All of the studies included in this review were from high-income countries. Data are lacking from populations in which the AOM incidence and risk of progression to mastoiditis is higher. Antibiotics caused unwanted effects such as diarrhoea, vomiting and rash and may also increase resistance to antibiotics in the community. It is difficult to balance the small benefits against the small harms of antibiotics in children with AOM. However, for most children with mild disease, an expectant observational approach seems justified.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Antibiotic versus placebo for acute otitis media in children

Patient or population: children with acute otitis media
Setting: primary and secondary care
Intervention: antibiotic versus placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Absolute effect (95% CI)	NNTB/NNTH (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk					
	Control	Antibiotic versus placebo					
Pain at 24 hours	Medium-risk population		RR 0.89 (0.78 to 1.01)	RD -5% (-10% to 0%)	n/a	1394 (6)	⊕⊕⊕⊕ high
	405 per 1000	360 per 1000 (316 to 409)					
Pain at 2 to 3 days	Medium-risk population		RR 0.70 (0.57 to 0.86)	RD -5% (-7% to -2%)	20 (14 to 50)	2320 (7)	⊕⊕⊕⊕ high
	215 per 1000	151 per 1000 (123 to 185)					
Pain at 4 to 7 days	Medium-risk population		RR 0.79 (0.66 to 0.95)	RD -5% (-9% to -1%)	20 (11 to 100)	1263 (7)	⊕⊕⊕⊕ high
	114 per 1000	90 per 1000 (75 to 108)					
Abnormal tympanometry - 4 to 6 weeks	Medium-risk population		RR 0.92 (0.83 to 1.01)	RD -4% (-8% to 0%)	n/a	2144 (7)	⊕⊕⊕⊕ high

	411 per 1000	**378 per 1000** (341 to 415)					
Abnormal tympanometry - 3 months	**Medium-risk population**		**RR 0.97** (0.76 to 1.24)	**RD -1%** (-7% to 5%)	**n/a**	**809** (3)	⊕⊕⊕⊕ **high**
	234 per 1000	**227 per 1000** (178 to 290)					
Vomiting, diarrhoea or rash	**Medium-risk population**		**RR 1.34** (1.16 to 1.55)	**RD 7%** (4% to 10%)	**14** (10 to 25)	**2023** (7)	⊕⊕⊕⊕ **high**
	196 per 1000	**263 per 1000** (227 to 304)					

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval (CI)) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI)
CI: confidence interval; RR: risk ratio; RD: risk difference; NNTB: number needed to treat to benefit; NNTH: number needed to treat to harm

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low quality: we are very uncertain about the estimate

BACKGROUND

Description of the condition

Acute otitis media (AOM) is one of the most frequent diseases in early infancy and childhood. AOM is defined as the presence of middle-ear effusion and a rapid onset of signs or symptoms of middle-ear inflammation, such as ear pain, otorrhoea or fever (Gates 2002) and has a high morbidity and low mortality (Stool 1989). Approximately 10% of children have an episode of AOM by three months of age and, by three years of age, approximately 50% to 85% of all children have experienced at least one AOM episode (Teele 1989). The peak age-specific incidence is between six and 15 months (Klein 1989).

Description of the intervention

Despite a large number of published clinical trials, there is no consensus regarding the most appropriate therapy of AOM; for example, the rates of use of antibiotics for AOM varies from 56% in the Netherlands (Akkerman 2005) to 95% in the USA and Canada (Froom 2001). One meta-analysis (Rosenfeld 1994) emphasises that AOM resolves spontaneously in most children. However, one semi-randomised trial of 1365 participants conducted in Sweden in 1954 (Rudberg 1954) reported a rate of mastoiditis of 17% in the untreated group versus none in the penicillin-treated groups. Over the past years, prescription strategies in which antibiotic treatment for acute respiratory infections such as AOM is delayed and instituted only if symptoms persist or worsen after several days have been advocated (AAP 2004).

How the intervention might work

AOM has a multifactorial pathogenesis. Mucosal swelling of the nasopharynx and Eustachian tube due to a viral upper respiratory tract infection can lead to Eustachian tube dysfunction with impaired clearance and pressure regulation of the middle ear. Prolonged dysfunction may be followed by aspiration of potential viral and bacterial pathogens from the nasopharynx to the middle ear. These pathogens might in turn provoke a host inflammatory response, which leads to the clinical manifestations of AOM such as ear pain, otorrhoea, fever and irritability. The predominant bacteria related to AOM are *Streptococcus pneumoniae* (*S. pneumoniae*), *Moraxella catarrhalis* (*M. catarrhalis*) and non-typeable *Haemophilus influenzae* (*H. influenzae*). Additionally, viral (co-)infection is known to worsen the clinical and bacteriological outcome of AOM (Arola 1990; Chonmaitree 1992). As bacteria are considered to play a predominant role in the causation of AOM-related symptoms, antibiotic treatment may accelerate clinical recovery and may reduce the number of complications related with AOM.

Why it is important to do this review

Although numerous randomised clinical trials (RCTs) on the effectiveness of antibiotic treatment in children with AOM have been performed over the past decades, consensus regarding the most appropriate treatment strategy is lacking. As symptoms consistent with AOM resolve spontaneously in the majority of children, an expectant observational approach might be justified. We therefore performed a systematic review to examine the effects of both immediate antibiotic treatment and an expectant observational approach in children with AOM. This is an update of a Cochrane review first published in 1997 (Glasziou 1997) and previously updated in 2009 (Sanders 2009).

OBJECTIVES

The aim of this review was to assess the usefulness of antibiotic treatment for AOM in children.

We attempted to determine to what extent antibiotic therapy was more effective than placebo and what, if any advantages, it offered to children in terms of symptom relief (pain), avoidance of complications (such as tympanic membrane perforations and severe complications such as mastoiditis) and longer-term hearing problems from middle-ear effusion (as measured by tympanometry or audiogram). We also assessed the effect of immediate antibiotic versus expectant observation to AOM. Moreover, we aimed to provide information on subgroups of children with AOM that benefit more or less from antibiotics.

METHODS

Criteria for considering studies for this review

Types of studies

RCTs of antimicrobial drugs versus placebo control. RCTs comparing immediate antibiotic versus expectant observation were also included.

Types of participants

Studies including children (aged from one month to 15 years) of either gender without ventilation tubes, suffering from AOM irrespective of the setting from which they were recruited.

Types of interventions

Antimicrobial drugs versus placebo control.
Immediate antibiotic versus expectant observation (also known as 'wait and see' or 'watchful waiting' or 'observation therapy'). This includes expectant observational approaches in which prescriptions may or may not be provided.

Types of outcome measures

We focused our data extraction on patient-relevant outcomes, that is, those symptoms or problems that are important to the patient's sense of well-being. While other end points, such as microbiological cure may enhance medical understanding of the disease process, decisions about treatment should focus on helping the patient.

Primary outcomes

1. Proportion of children with pain at various time points (24 hours, two to three days, four to seven days).

Secondary outcomes

1. Abnormal tympanometry findings at various time points (four to six weeks and three months) as surrogate measure for hearing problems caused by middle-ear fluid.
2. Tympanic membrane perforation.
3. Contralateral otitis (in unilateral cases).
4. AOM recurrences.
5. Serious complications related to AOM such as mastoiditis and meningitis.
6. Adverse effects likely to be related to the use of antibiotics such as vomiting, diarrhoea or rash.

Search methods for identification of studies

Electronic searches

For this update we searched the Cochrane Central Register of Controlled Trials (CENTRAL) 2012, Issue 10, part of *The Cochrane Library* (accessed 8 November 2012), which contains the Acute Respiratory Infections (ARI) Group's Specialised Register, MEDLINE (June 2008 to October week 4, 2012), EMBASE (June 2008 to November 2012), Current Contents (2008 to November 2012), CINAHL (2008 to November 2012) and LILACS (2008 to November 2012). See Appendix 1 for details of previous searches. We used the following search strategy to search CENTRAL and MEDLINE. The MEDLINE search was combined with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity- and precision-maximising version (2008 revision); Ovid format (Lefebvre 2011). The search strategy was adapted to search EMBASE (Appendix 2), Current Contents (Appendix 3), CINAHL (Appendix 4) and LILACS (Appendix 5).

MEDLINE (Ovid)

1 exp Otitis Media/
2 otitis media.tw.
3 glue ear*.tw.
4 (middle ear adj5 (infect* or inflam*)).tw.
5 (ome or aom).tw.
6 or/1-5
7 exp Anti-Bacterial Agents/
8 Drug Therapy/
9 Anti-Infective Agents/
10 antibiotic*.tw.
11 antibacterial*.tw.
12 exp Ampicillin/
13 exp Cephalosporins/
14 exp Macrolides/
15 exp Penicillins/
16 (ampicillin* or cephalosporin* or macrolide* or penicillin* or amoxicillin* or amoxycillin* or cefdinir or cefpodoxime or cefuroxime or azithromycin or clarithromycin or erythromycin*).tw,nm.
17 or/7-16
18 6 and 17
There were no language or publication restrictions.

Searching other resources

We checked ClinicalTrials.gov (clinicaltrials.gov/) for ongoing trials (13 November 2012). To increase the yield of relevant studies, we inspected the reference lists of all identified studies and reviews.

Data collection and analysis

Selection of studies

One review author (RPV) screened titles and abstracts obtained from the database searches. Two review authors (RPV, MMR) reviewed the full text of the potentially relevant titles and abstracts against the inclusion criteria.

Data extraction and management

Two review authors (RPV, MMR) extracted data from the included studies. We resolved disagreements by discussion.

Assessment of risk of bias in included studies

Two review authors (RPV, MMR) independently assessed the methodological quality of the included trials. We resolved any disagreements by discussion. We assessed the methodological quality of the included studies as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). As a consequence, methodological quality assessment was based on random sequence generation, allocation concealment, blinding, completeness of data and outcome assessment. Results of the risk of bias assessment are presented in a 'Risk of bias' summary (Figure 1) and a 'Risk of bias' graph (Figure 2).

Figure 1. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

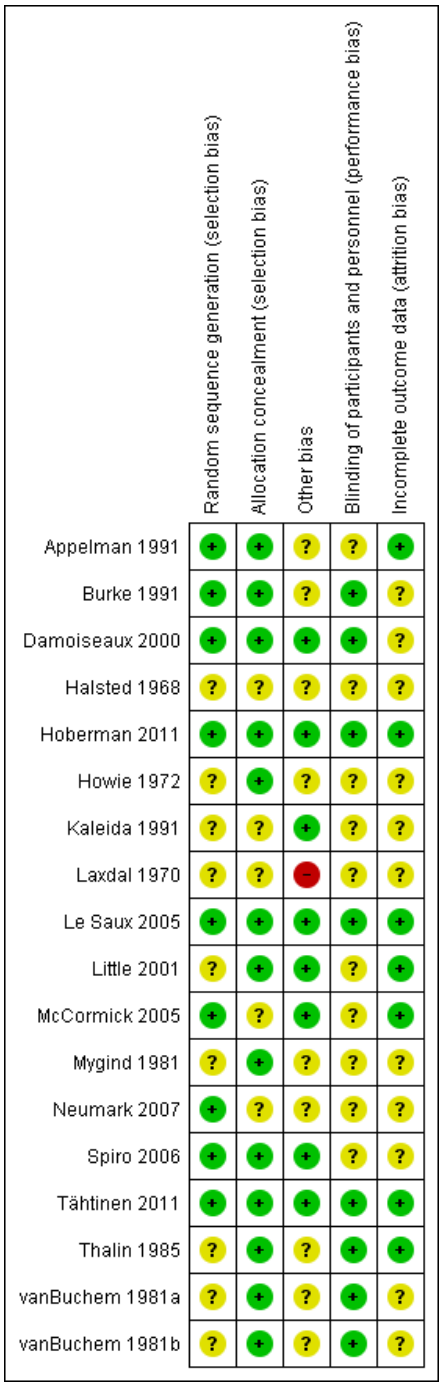
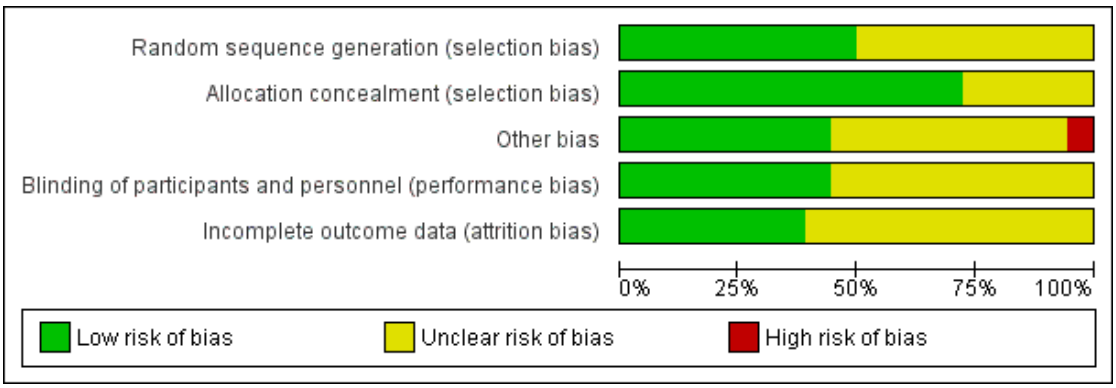


Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Measures of treatment effect

We expressed dichotomous outcomes as risk ratios (RR) and risk difference (RD) with 95% confidence intervals (CIs). Additionally, number needed to treat for an additional beneficial outcome (NNTB) and number needed to treat for an additional harmful outcome (NNTH) were calculated (1/(absolute risk in exposed minus absolute risk in unexposed)).

Unit of analysis issues

We did not identify any studies with non-standard designs, such as cross-over trials and cluster-randomised trials.

Dealing with missing data

We tried to contact the trial authors to provide additional information in case of missing data.

Assessment of heterogeneity

We used the Chi^2 test, the I^2 statistic and visual inspection of the forest plots to assess heterogeneity. When statistical heterogeneity was present ($P < 0.1$) we re-analysed the data using the random-effects model. For the outcome of pain, the magnitude of baseline risk and heterogeneity was explored using L'Abbé plots (graph of the proportion of participants with an outcome by the proportion of participants without an outcome).

Assessment of reporting biases

We assessed reporting bias using a funnel plot.

Data synthesis

We calculated treatment differences by the Mantel-Haenszel method using a fixed-effect or random-effects (when statistical heterogeneity was present) model.

Subgroup analysis and investigation of heterogeneity

The publication of Rovers 2006 describes the results of an individual patient data (IPD) meta-analysis that has been performed on a subset of trials included in this review (six trials including 1643 children aged six months to 12 years with AOM) to identify subgroups of children with AOM who might benefit more than others from treatment with antibiotics. Extensive details on methods and results of this IPD meta-analysis can be found in the original article (Rovers 2006). The primary outcome was a prolonged course of AOM defined as having either residual pain or fever (> 38 ºC) at three to seven days. Potential subgroups were selected on the basis of a multivariable prediction tool. The independent baseline predictors, that is, age (< two years versus > two years), fever and bilateral AOM (yes versus no), were used to study whether those at risk of a prolonged course also benefited more from treatment with antibiotics. In addition, otorrhoea (yes versus no) at baseline was studied as this appears to be a clinically relevant outcome that occurs too infrequently to be identified as an independent predictor. To assess whether the effect of antibiotics was

modified by age, bilateral disease, otorrhoea, or a combination of these, a fixed-effect logistic regression analysis was performed. In this model, antibiotics (yes versus no), the potential effect modifier (age, bilateral disease, otorrhoea, or a combination of these), a dummy for the particular study and an interaction term (antibiotics * potential effect modifier) were included as independent variables and a prolonged course at three to seven days was the dependent variable. If a significant interaction effect was found, stratified analyses were performed to study the rate ratios and rate differences within each stratum of the subgroups.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Results of the search

This is an update of a Cochrane review first published in 1997 (Glasziou 1997) and updated in 2009 (Sanders 2009). With the updated search (June 2008 to November week 2, 2012) we retrieved a 583 records. Removing duplicates left 356. After screening titles and abstracts, we identified six potentially eligible studies. We obtained their full-text papers and excluded four studies as they studied the effectiveness of short- versus long-course antibiotics (Arguedas 2011), a single-dose antibiotics with slow release versus immediate-release formulations (Liu 2011), two different types of antibiotics (Casey 2012) and immediate versus delayed antibiotic prescription based on a secondary analysis of a placebo-controlled trial (Tähtinen 2012). This left two new trials eligible for inclusion for the review of antibiotics against placebo (Hoberman 2011; Tähtinen 2011). These studies included children < 35 months of age and provided data on pain (Tähtinen 2011), contralateral otitis, late recurrences (Hoberman 2011), perforation and adverse events (Hoberman 2011; Tähtinen 2011). We identified no additional eligible trials after scanning the reference lists of full-text papers. In this updated review, the Laxdal 1970 trial has been removed from the review of antibiotics against placebo and added to the review of immediate antibiotics versus expectant observation. No new trials were identified for the review of immediate antibiotics compared with expectant observation. Furthermore, we did not identify any ongoing trials.

Included studies

Twelve trials including 3317 children (3854 AOM episodes) were eligible for the review of antibiotics against placebo. The children were aged 12 years and younger and 50% to 60% of included children were male. One trial (vanBuchem 1981a; vanBuchem 1981b) had a 2 x 2 factorial design resulting in four treatment groups: (1) sham myringotomy plus antibiotics; (2) sham myringotomy plus placebo; (3) myringotomy plus antibiotics; and (4) myringotomy plus placebo. We used all arms of this trial: vanBuchem 1981a includes the sham myringotomy plus antibiotic and the sham myringotomy plus placebo arms, whereas vanBuchem 1981b includes the myringotomy plus antibiotic and myringotomy plus placebo arms. We were able to derive outcome data for our review from 11 trials. One trial (Howie 1972) did not report any patient-relevant outcomes such as symptoms, hearing problems, complications or adverse events.

Five trials (Laxdal 1970; Little 2001; McCormick 2005; Neumark 2007; Spiro 2006) including a total of 1149 children aged 15 years and younger compared different treatment approaches. In two of these trials (Little 2001; Spiro 2006) provision of an immediate antibiotic script was compared with an antibiotic script with instructions not to commence antibiotic treatment unless the child was not better or was worse at 48 hours (Spiro 2006) or 72 hours (Little 2001). In these trials, 24% (36/150) and 38% (50/132) of children in the delayed arms reported using antibiotics at some stage during the illness. Data on pain at days four to six could be derived from these two trials (Little 2001; Spiro 2006). The data on pain of the trial of Little et al. (Little 2001) has been derived from data of the IPD meta-analysis (Rovers 2006). The other three trials (Laxdal 1970; McCormick 2005; Neumark 2007) compared immediate antibiotics with a watchful waiting approach. In the trial by Laxdal 1970, children in the control group were closely monitored, especially during the first 48 hours and particularly when severe involvement was evident. This trial did not report outcome data that could be used for this review. In the trial by McCormick 2005, antibiotics were administered to the watchful waiting group if a child returned to the office with a treatment failure or recurrence (four children in the expectant observation group had received antibiotics by day four). The author provided data on pain for this trial. In the trial by Neumark 2007, 5% (4/87) of children randomised to the watchful waiting group received antibiotics due to treatment failure. This trial reported on the number of children with moderate or severe pain between days three to seven.

Excluded studies

We excluded 11 trials after reviewing the full text. Three trials were non-randomised studies (Ostfeld 1987; Rudberg 1954; vanBuchem 1985) and three other trials had no comparison of antibiotic to placebo or expectant observation (Casey 2012; Engelhard 1989; Sarrell 2003). Two trials studied the effectiveness of short- versus long-course antibiotics (Arguedas 2011; Chaput 1982), one trial studied a single-dose antibiotics with slow versus immediate-release formulations (Liu 2011), whereas another trial was conducted in children with ventilation tubes (Ruohola 2003). Moreover, one trial report was excluded as this study reported on

the effectiveness of immediate versus delayed antibiotic prescription based on a secondary analysis of a placebo-controlled trial (Tähtinen 2012).

Risk of bias in included studies

The methodological quality of the included studies was generally high. For further details on the risk of bias in included studies see 'Risk of bias' summary (Figure 1) and 'Risk of bias' graph (Figure 2).

Allocation

Concealment of allocation was adequately described in nine of the 11 included trials comparing antibiotics with placebo that reported patient-relevant outcomes and two out of five trials comparing immediate antibiotics with expectant observation. Random sequence generation was adequate in six of the 11 trials and in three of the five included trials, respectively.

Blinding

All included trials in the review of antibiotics against placebo stated that they were double-blinded. However, blinding was judged to be adequate in eight of the 11 included trials reporting patient-relevant outcomes. All five trials comparing immediate antibiotics with expectant observation were open label trials. As a consequence, reporting of the child's symptoms by parents was not blinded in these trials. However, investigators were blinded in two of the five trials (McCormick 2005; Spiro 2006).

Incomplete outcome data

The loss to follow-up was below 5% in six of the 11 trials comparing antibiotics with placebo that reported patient-relevant outcomes. Loss to follow-up was high in three of the 11 trials with a total loss to follow-up of 15% (vanBuchem 1981a; vanBuchem 1981b), 7% (Kaleida 1991) and 12% (Damoiseaux 2000), respectively. However, one of these trials included all randomised patients in the primary analysis at day four (Damoiseaux 2000). In two of the 11 trials (Halsted 1968; Mygind 1981) the total number of loss to follow-up / exclusions are described but it was unclear from which treatment group children were excluded. For the review of immediate antibiotics against expectant observation, the loss to follow-up was below 5% in two of the five trials (McCormick 2005; Neumark 2007). The total loss to follow-up in the other trials was 11% (Laxdal 1970), 10% (Little 2001) and 6% (Spiro 2006).

Selective reporting

Seven of the 11 included trials comparing antibiotics with placebo that did report patient-relevant outcomes used intention-to-treat (ITT) analyses, while in the other four this was not clear (Halsted 1968; Mygind 1981; Thalin 1985; vanBuchem 1981a; vanBuchem 1981b). For the review of immediate antibiotics versus expectant observation, three of the five included trials used ITT analyses, while this was not clear in the other two trials (Laxdal 1970; Neumark 2007).

Other potential sources of bias

No other potential sources of bias could be detected in the included trials.

Effects of interventions

See: **Summary of findings for the main comparison**

Pain

The combined results of the trials revealed that by 24 hours from the start of treatment, 60% of the children had recovered whether or not they had placebo or antibiotics. At days two to seven, 82% of children had spontaneously recovered (pooled control groups). Antibiotics achieved a 30% relative reduction in the risk of pain at days two to three (95% CI 14% to 43%) and 21% in the risk of pain at days four to seven (95% CI 5% to 34%) (Analysis 1.1). This means 5% fewer children had pain after two to three days (95% CI -7% to -2%) and four to seven days (95% CI -9% to -1%), respectively. Therefore, 20 (95% CI 14 to 40) children needed to be treated to prevent one child experiencing pain at days two to seven. Plots of the event rate (pain) in the treatment and control groups for each study on the various time points (two to three days and four to seven days) are reported in Figure 3 and Figure 4. The funnel plot for pain at the various time points did not reveal asymmetry (Figure 5).

Figure 3. L'Abbe plot of the rates of pain at two to three days for the placebo (control) versus antibiotic (experimental) group.

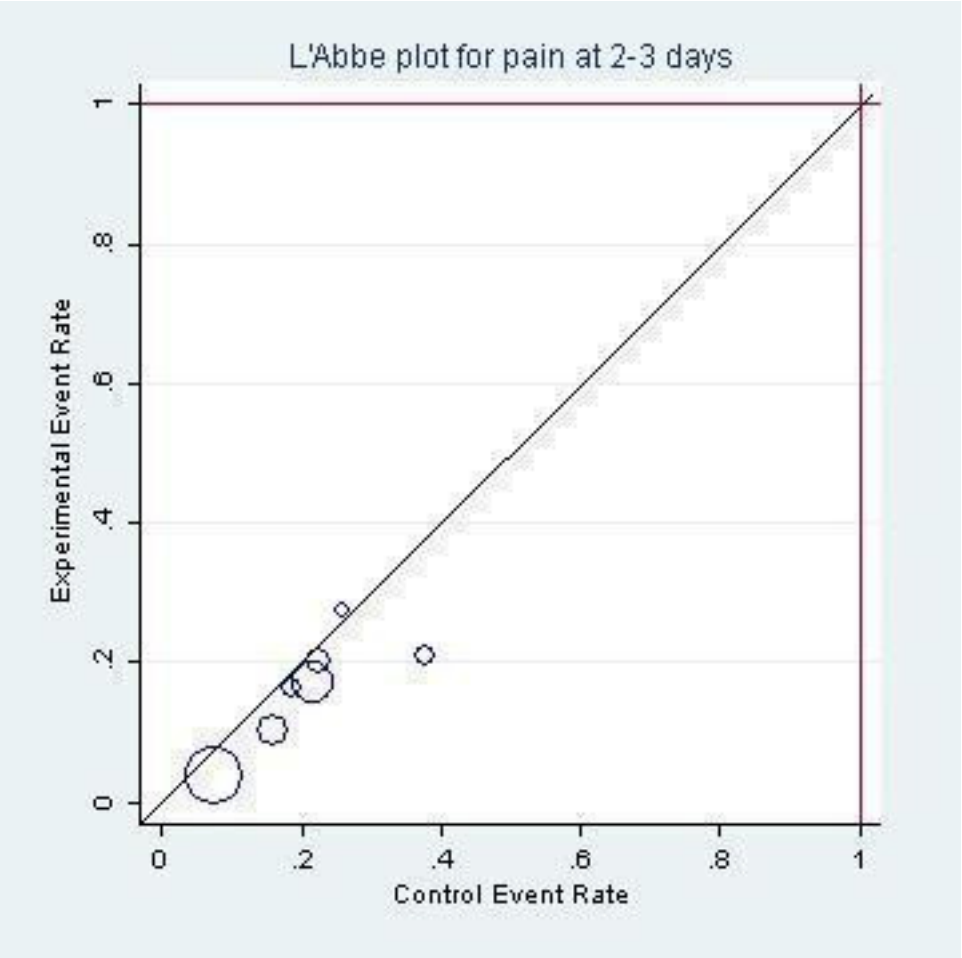


Figure 4. L'Abbe plot of the rates of pain at four to seven days for the placebo (control) versus antibiotic (experimental) group.

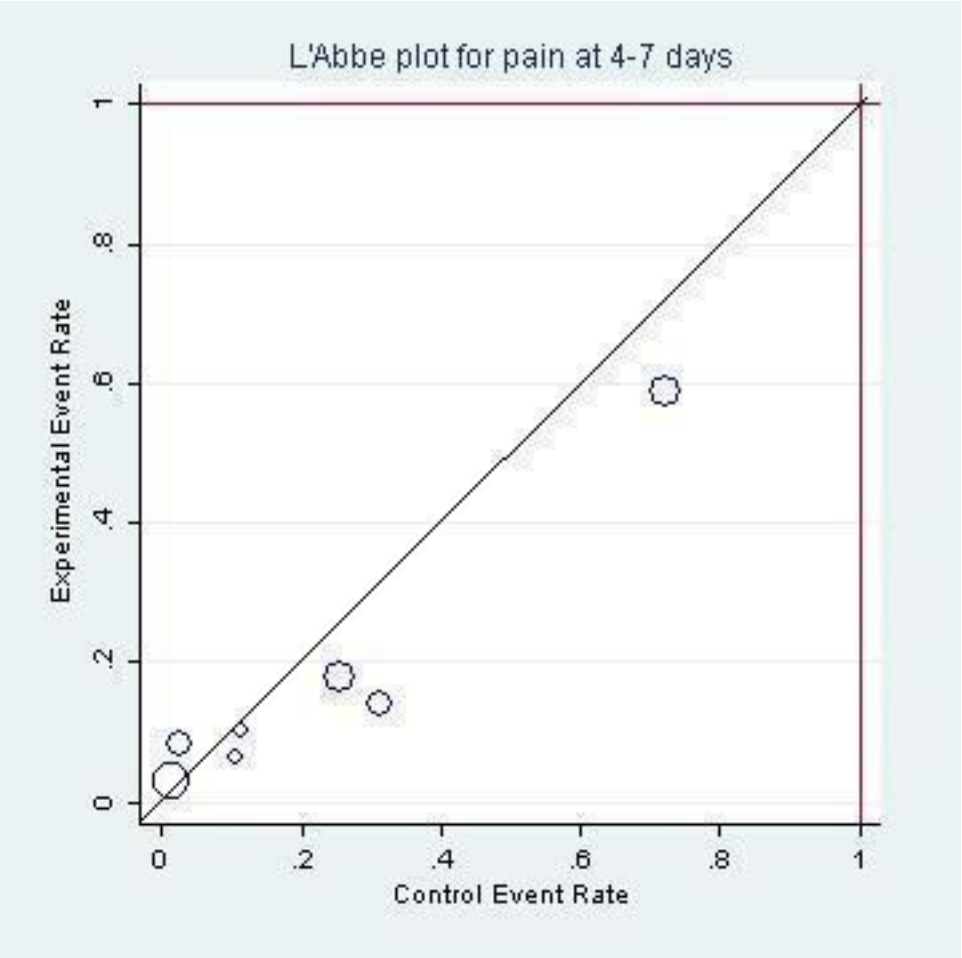
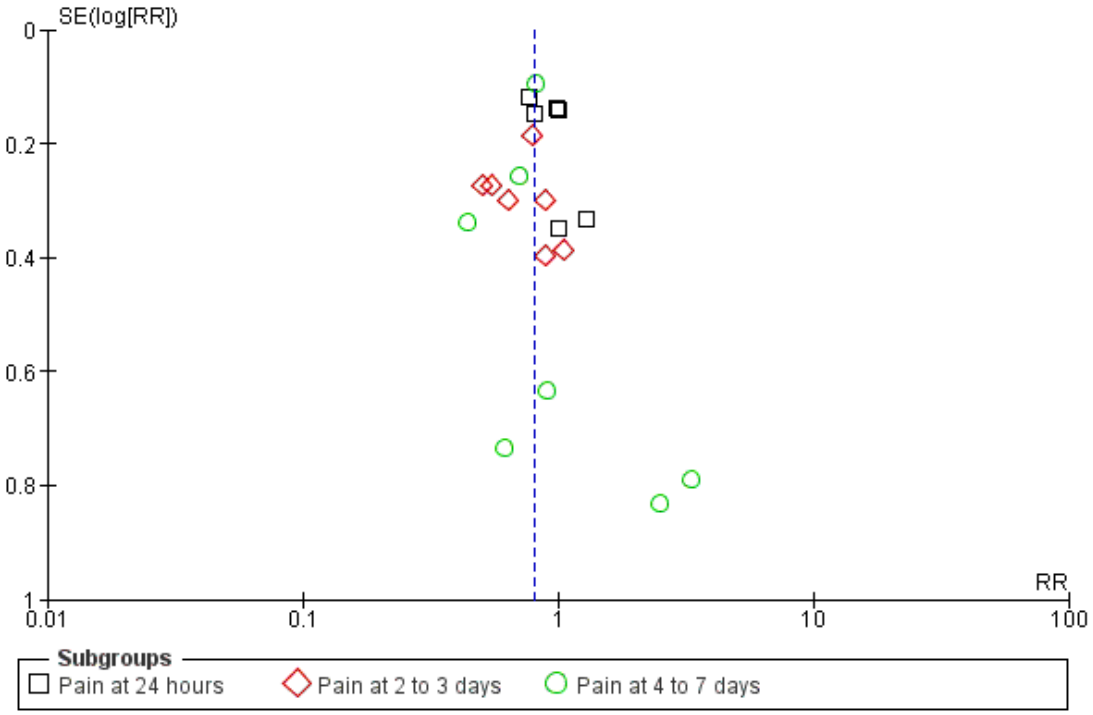


Figure 5. Funnel plot of comparison: 1 Antibiotic versus placebo, outcome: 1.1 Pain.



Hearing (as measured by tympanometry)

In the seven trials that measured tympanometry there was no clinically or statistically significant difference in tympanometry results at four to six weeks or three months after the acute episode, suggesting no effects on hearing (Analysis 1.2). However, audiometry was done in only two studies and incompletely reported. The two studies that used audiograms were: (i) vanBuchem 1981a reported that, "After one month, 31% of the patients showed an air/bone gap of more than 20 dB. After two months, this was still the case with 19% of the patients. Here again, there were no significant differences between the groups". (ii) Kaleida 1991 stated that "Analysis of hearing acuity in children two years of age and older indicated that elevated hearing thresholds ... bore no apparent relationship ... to mode of treatment (amoxicillin versus placebo)".

Tympanic membrane perforation

Four trials reported on this outcome. Antibiotic treatment was associated with a reduction of tympanic membrane perforation as compared to placebo (Analysis 1.3). However, absolute benefits of antibiotics appeared to be small (RD -3%; 95% CI -6% to -1%). Therefore, 33 children (95% CI 17 to 100) needed to be treated to prevent one child experiencing a tympanic membrane perforation.

Progression of symptoms (contralateral otitis or late recurrence)

Antibiotics reduced the development of contralateral otitis (Analysis 1.4) but was not associated with a reduction of late AOM recurrences (Analysis 1.5). AOM recurrence was common. Burke 1991 stated "The mean number of recorded recurrences of otitis media or acute red ear was 0.70 (range 0 to 4) in the antibiotic group and 0.63 (range 0 to 7) in the placebo group and this difference was not significant (difference 0.06; 95% CI -0.22 to 0.339)." Six other trials reported the proportions who relapsed; combined, these give an RR of 0.93 (95% CI 0.79 to 1.10), which is consistent with Burke's findings.

Serious complications

Few serious complications occurred in either the antibiotic treatment group or the control group. In just over 3000 children studied, only one case of mastoiditis occurred in both the antibiotic (Mygind 1981) and the placebo (Hoberman 2011) group.

Moreover, one child suffered from meningitis (Damoiseaux 2000), pneumococcal bacteraemia and radiologically confirmed pneumonia (Hoberman 2011) in the placebo group and one child had transient facial paralysis in the antibiotic group (Kaleida 1991). Hence, the applicability of these findings to groups of children in whom serious complications such as mastoiditis is common is uncertain. One of the excluded studies (Rudberg 1954) did report high rates of mastoiditis. This was an open, semi-randomised study conducted in Sweden in 1954. Patients were randomised by case-sheet number but a proportion (about 30 of 220) requested and were granted, entry to the penicillin group. The rate of mastoiditis was 17% in the untreated group versus 1.5% in the sulphonamide-treated group and 0% in the penicillin-treated group. The biases of this study (semi-randomisation and unblinded outcome assessment) are unlikely to explain such a large difference.

Adverse events (vomiting, diarrhoea or rash)

The occurrence of vomiting, diarrhoea or rash was reported in seven trials. Antibiotics resulted in a 34% (95% CI 16% to 55%) relative increase in risk of adverse events; 27% (274/1002) of children treated with antibiotics versus 20% (206/1021) of children treated with placebo experienced vomiting, diarrhoea or rash (Analysis 1.6). The NNTH was 14.

Immediate antibiotics versus expectant observation

At days three to seven, there was no difference in pain between children receiving an immediate antibiotic prescription and those randomised to observation with or without an antibiotic prescription (RR 0.75; 95% CI 0.50 to 1.12) (Analysis 2.1). No serious complications occurred in either the antibiotic group or the expectant observation group. One trial (Neumark 2007) did report on tympanic membrane perforations at three months but no perforation occurred in either groups (Analysis 2.2). Additionally, no difference in AOM recurrence was observed between patients receiving immediate antibiotics and those receiving expectant observational treatment (Analysis 2.3). Immediate antibiotic prescribing was associated with a substantial increased risk of vomiting, diarrhoea or rash as compared with expectant observation (RR 1.71; 95% CI 1.24 to 2.36; RD 12%; 95% CI 5% to 19%) (Analysis 2.4). The NNTH is 9.

Individual patient data meta-analysis to identify children most likely to benefit from antibiotic treatment

Main findings of the IPD meta-analysis of Rovers 2006 were that significant effect modifications were noted for age and bilateral AOM and for otorrhoea; in children aged less than two years with bilateral AOM, 55% of the control group and 30% of the antibiotics group still had pain, fever or both at days three to seven (risk reduction of 25%; 95% CI 14% to 36%; NNTB 4). In children aged two years or older with bilateral AOM the risk reduction was 12% (95% CI -1% to 25%; P value for interaction = 0.022). Among children with otorrhoea, 60% of those in the control group had pain, fever or both at days three to seven versus 24% in the antibiotics group (risk reduction of 36%; 95% CI 19% to 53%; NNTB 3) The reduction in risk among those without otorrhoea was 14% (95% CI 5% to 23%; NNTB 8; P value for interaction = 0.039). No differences were identified for age alone.

DISCUSSION

Summary of main results

This review reveals that antibiotics have no early impact on pain and only modest overall impact on the clinical course of AOM. However, in applying these results, there are a number of issues to consider, including the individual potential for serious complications and subgroups of children in whom there may be greater benefits.

Overall completeness and applicability of evidence

Does the effect vary in different clinical groups? Our NNTB of 20 for pain at days two to three and pain at days four to seven is for the 'average' case and may vary in subgroups. Several studies (Appelman 1991; Burke 1991; Damoiseaux 2000; Hoberman 2011; Tähtinen 2011) have reported higher rates of failure of placebo treatment among children less than two years of age and those with bilateral disease and another trial (Little 2001) has suggested that most benefit is seen in children with high fever or vomiting. Moreover, some studies (Barkai 2009; McCormick 2007) found that children with bilateral AOM differ with regard to clinical and microbiological (increased presence of (non-typeable) *H influenzae*) characteristics as compared to children with unilateral AOM. However, the IPD meta-analysis (Rovers 2006) demonstrated that the relative effects of antibiotics were not significantly modified by either age or bilateral disease alone but the absolute differences were larger in the younger patients (< two years) with bilateral disease and in children with both AOM and otorrhoea. Further analysis of these data has shown that age younger than two years is an independent predictor of the development of asymptomatic middle-ear effusion (Koopman 2008). This analysis also found that antibiotic therapy has a marginal effect on the development of asymptomatic middle-ear effusion in children with AOM.

Does the impact vary by duration of antibiotics? Most trials use seven days of antibiotic treatment. One recent meta-analysis of short (< seven days) versus long (> seven days) course antibiotics (Kozyrskyj 2010) reported that risk of treatment failure at one

month was higher with short courses of antibiotics (OR 1.34; 95% CI 1.15 to 1.55). However, the absolute difference in treatment effect was small (3%) and short-course antibiotics was associated with a statistically significant reduction in gastrointestinal adverse events.

What are the potential consequences of not using antibiotics? Besides the immediate pain of AOM, there are some more serious complications. Though only two cases of mastoiditis were reported in the included trials (one child received antibiotics and one child was assigned to placebo), a semi-randomised trial in Sweden in 1954 (Rudberg 1954) reported a rate of 17% in the untreated group versus none in the penicillin-treated groups. In populations or sub-populations where mastoiditis is still judged a frequent problem, such as in some low-income countries (Berman 1995), antibiotic treatment would be strongly advised.

Of note, is an article that revealed that doctors commonly overdiagnose AOM (Rothman 2003). What effect might this have on the efficacy of antibiotics (or any treatment)? One effect will be to blunt any treatment effect by dilution (from the cases of non-AOM). The results of two recently performed trials (Hoberman 2011; Tähtinen 2011) in which AOM has been diagnosed with the use of stringent criteria (including pneumatic otoscopic examination in one trial (Tähtinen 2011)) underline this phenomenon. Nevertheless, physicians in daily practice are likely to use the same diagnostic methods (perhaps even less stringent) as used in the majority of the included trials of this review. As a consequence, the efficacy of antibiotics reported in this review is likely to be a true reflection of the efficacy in actual clinical practice. However, if new and more accurate diagnostic procedures are introduced in future daily practice, then the current estimate of efficacy will have to be reconsidered.

Quality of the evidence

The methodological quality of the included studies was generally high. Almost all included trials used adequately concealed allocation, while random sequence generation was adequate in six of the 11 trials comparing antibiotics with placebo, and in three of the five included trials comparing immediate antibiotics with expectant observation. Blinding was judged to be adequate in eight of the 11 included trials for the review of antibiotics versus placebo, while investigators were blinded in two of the five trials comparing immediate antibiotics with expectant observation. The loss to follow-up was less than 5% in six of the 11 trials comparing antibiotics. Loss to follow-up was high in three of the 11 trials comparing antibiotics with placebo with a total loss to follow-up varying from 7% to 15% and in three of the five trials comparing immediate antibiotics with expectant observation with a total loss to follow-up varying from 6% to 11%.

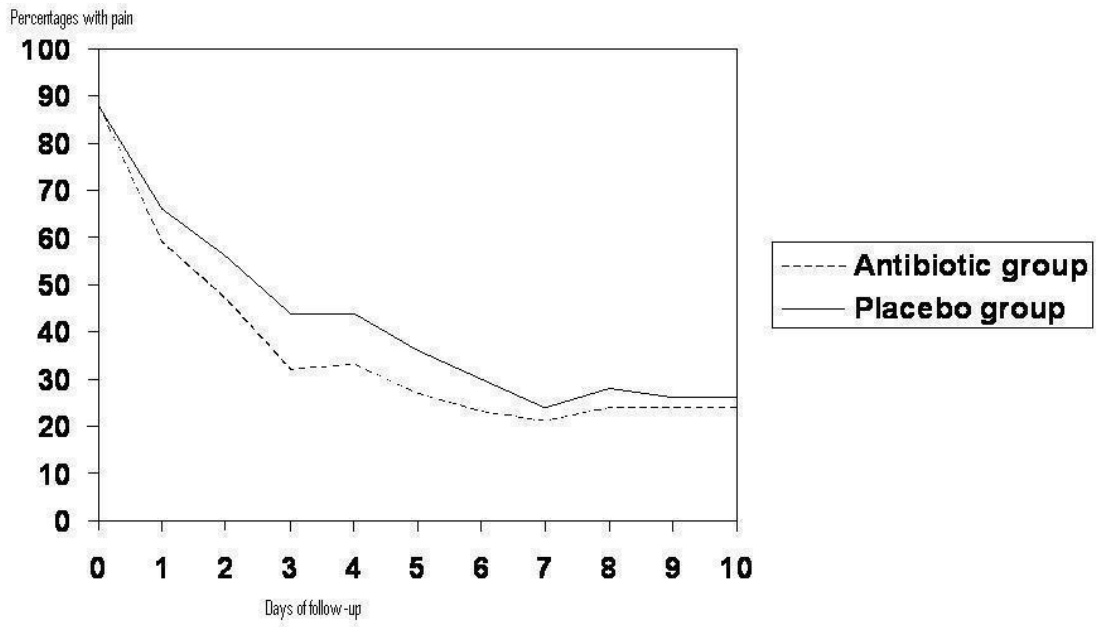
Potential biases in the review process

There was some clinical heterogeneity among the included trials. For example, patients were recruited from different settings (general practice, otolaryngology, paediatric clinics). However, the majority of included trials did use a diagnostic method (clinical diagnosis of AOM as inclusion criteria) that resembles daily clinical practice. Besides, duration and dosage of the antibiotic treatment varied to some extent. For the review of antibiotics against placebo, the duration of antibiotic treatment varied from seven to 14 days. However, we do not consider this as a major drawback since most trials used seven days of antibiotic treatment and current evidence indicates only a small absolute treatment difference (3%) in treatment failure at one month in favour of long (> seven days) versus short (< seven days) course antibiotics. Moreover, the primary outcome of this review (proportions of children with pain) is reported within the first seven days of antibiotic treatment. In addition, we assessed funnel plots for potential reporting biases for primary analysis (Figure 5). No asymmetry could be detected based on the included trials.

Agreements and disagreements with other studies or reviews

This review demonstrated that at 24 hours 60% of children had recovered spontaneously and that the majority had recovered in the following two to seven days regardless of whether they had received placebo or antibiotics. However, the IPD meta-analysis that included six of the trials included in this review, revealed a slower rate of recovery (Figure 6) with only 22% of children experiencing spontaneous recovery at 24 hours (Rovers 2006). There are a number of possible explanations for this. First, data from older trials was not included in the IPD meta-analysis and consequently the study population may reflect a higher threshold of doctor visitation; for example, the children may be 'sicker' or presenting to the doctor later in the course of their illness. Variation in the definitions of pain/no pain cut-offs among the trials included in the reviews may also explain some of this variation. From the IPD meta-analysis survival curve (Figure 6) it can be seen that antibiotics had greatest effect compared to placebo at day three.

Figure 6. Percentage with pain based on the subset of six studies included in the IPD Meta-analysis (Rovers et al 2006).



A previous meta-analysis had examined the question of whether antibiotics were indicated for AOM in children and concluded that the answer is a qualified "yes" (Rosenfeld 1994). It estimated an NNTB of seven for "primary control" (complete clinical resolution), compared with our NNTB of 20 for symptom relief. The difference may be the consequence of our focus on patient-oriented outcomes, such as pain, rather than clinical signs, such as eardrum appearance. The previous systematic review suggests that where mastoiditis is not a concern, primary care physicians could weigh the benefits against the risks of adverse effects from antibiotics with their patients. This statement is in agreement with the findings of our review as adverse events such as diarrhoea, vomiting or rash were more common in children receiving antibiotics. In the IPD meta-analysis (Rovers 2006) the most commonly described adverse effect of antibiotic treatment was diarrhoea ranging from 2% to 14% in controls and from 4% to 21% in those given antibiotics. Occurrence of rash ranged from 2% to 6% in the control groups and from 1% to 8% in the antibiotic groups. Bacterial resistance to antibiotics is also a consideration, with an association between antibiotic use and resistant bacteria demonstrated for many important pathogens (Arnold 2005).

Several trials (Laxdal 1970; Little 2001; McCormick 2005; Neumark 2007; Spiro 2006) have evaluated a management approach for AOM in which an expectant observational approach is used. In one of these trials (Little 2001) pain and malaise on day three were greater among those randomised to receive an antibiotic prescription with advice to fill it only if there was no improvement after 72 hours compared to those receiving immediate antibiotics. In a long-term follow-up of this trial (Little 2006) no difference was found between delayed and immediate treatment groups in ear function and ear pain at three and 12 months. Another study using a similar prescribing approach and examining clinical outcomes on days four to six found no difference between immediate and delayed antibiotic groups (Spiro 2006). In the third study (McCormick 2005), immediate antibiotic treatment was associated with decreased numbers of treatment failures and improved symptom control at day four and day 12 compared to those allocated to expectant observation with no prescription. Neumark 2007 in a similar comparison found that immediate antibiotics provided some symptomatic benefit; children who received antibiotics had less pain, used fewer analgesics and consulted less during the first seven days. Meta-analysis of data from these four trials found no difference in pain between immediate antibiotics and expectant observational approaches at days three to seven. Another review (Spurling 2010), which evaluated the effect of delayed versus immediate or no antibiotics for respiratory infections and which included two studies on AOM (Little 2001; Spiro 2006) concluded that immediate antibiotics was the strategy most likely to provide the best clinical outcomes for AOM. One randomised study (Chao 2008) found that observation therapy with or without a prescription in children with AOM was well accepted by

parents. Antibiotic use was less in those randomised to observation without prescription and no complications were reported.

AUTHORS' CONCLUSIONS

Implications for practice

Antibiotics produce a small reduction in the number of children with pain at two to three and four to seven days from assessment and reduce the number of tympanic membrane perforations. However, in high-income countries, most cases of AOM spontaneously remit without complications and the NNTB is 20 for pain at two to three and four to seven days and 33 for tympanic membrane perforation. These benefits must be weighed against the possible harms: for every 14 children treated with antibiotics one child experienced an adverse event (such as vomiting, diarrhoea or rash) that would not have occurred if antibiotics were withheld. Therefore management should emphasise advice about adequate analgesia and the limited role for antibiotics. Antibiotics are most useful in children under two years of age with bilateral AOM, or with both AOM and otorrhoea. For most other children with mild disease, an expectant observational approach seems justified. Cates has developed an appropriate handout and tested this together with an optional antibiotic prescription (Cates 1999). The handout is available at www.nntonline.net/ebm/main˙pages/AOM.asp (accessed 22 November 2012).

Implications for research

Further research is needed to determine if it is possible to predict which children are more likely to suffer from the complications of AOM.

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REFERENCES

References to studies included in this review

Appelman 1991 *{published data only}*

* Appelman CL, Claessen JQ, Touw Otten FW, Hordijk GJ, de Melker RA. Co-amoxiclav in recurrent acute otitis media: placebo controlled study. *BMJ* 1991;**303**:1450–2.
Appelman CL, Claessen JQ, Touw Otten FW, Hordijk GJ, de Melker RA. Severity of inflammation of tympanic membrane as predictor of clinical course of recurrent acute otitis media. *BMJ* 1993;**306**:895.
Claessen JQ, Appelman CL, Touw Otten FW, de Melker RA, Hordijk GJ. Persistence of middle ear dysfunction after recurrent acute otitis media. *Clinical Otolaryngology* 1994; **19**:35–40.

Burke 1991 *{published data only}*

Burke P, Bain J, Robinson D, Dunleavey J. Acute red ear in children: controlled trial of non-antibiotic treatment in general practice. *BMJ* 1991;**303**:558–62.

Damoiseaux 2000 *{published data only}*

Damoiseaux RAMJ, van Balen FAM, Hoes AW, Verheij TJM, de Melker RA. Primary care based randomised, double blind trial of amoxicillin versus placebo for acute otitis media in children aged under 2 years. *BMJ* 2000;**320**: 350–4.

Halsted 1968 *{published data only}*

Halsted C, Lepow ML, Balassanian N, Emmerich J, Wolinsky E. Otitis media: clinical observation, microbiology and evaluation of therapy. *American Journal of Diseases of Children* 1968;**115**(5):542–51.

Hoberman 2011 *{published data only}*

Hoberman A, Paradise JL, Rockette HE, Shaikh N, Wald ER, Kearney DH, et al.Treatment of acute otitis media in children under 2 years of age. *New England Journal of Medicine* 2011;**364**(2):105–15.

Howie 1972 *{published data only}*

Howie VM, Ploussard JH. Efficacy of fixed combination antibiotics versus separate components in otitis media: effectiveness of erythromycin estolate, triple sulfonamide, ampicillin, erythromycin estolate-triple sulfonamide, and placebo in 280 patients with acute otitis media under two and one-half years of age. *Clinical Pediatrics* 1972;**11**(4): 205–14.

Kaleida 1991 *{published data only}*

Kaleida PH, Casselhrant ML, Rockette HE, Paradise JL, Bluestone CD, Blatter MM, et al.Amoxicillin or myringotomy or both for acute otitis media: results of a randomized clinical trial. *Paediatrics* 1991;**87**(4):466–74.

Laxdal 1970 *{published data only}*
Laxdal OE, Merida J, Jones RHT. Treatment of acute otitis media: a controlled study of 142 children. *Canadian Medical Association Journal* 1970;**102**(3):263–8.

Le Saux 2005 *{published data only}*
Le Saux N, Gaboury I, Baird M, Klassen TP, MacCormick J, Blanchard C, et al.A randomized, double-blind, placebo-controlled noninferiority trial of amoxicillin for clinically diagnosed acute otitis media in children 6 months to 5 years of age. *Canadian Medical Association Journal* 2005;**172**(3): 335–41.

Little 2001 *{published data only}*
Little P, Gould C, Williamson I, Moore M, Warner G, Dunleavey J. Pragmatic randomised controlled trial of two prescribing strategies for childhood acute otitis media. *BMJ* 2001;**322**:336–42.

McCormick 2005 *{published data only}*
McCormick DP, Chonmaitree T, Pittman C, Saeed K, Friedman NR, Uchida T, et al.Nonsevere acute otitis media: a clinical trial comparing outcomes of watchful waiting versus immediate antibiotic treatment. *Pediatrics* 2005;**115** (6):1455–65.

Mygind 1981 *{published data only}*
* Mygind N, Meistrup-Larsen K-I, Thomsen J, Thomsen VF, Josefsson K, Sorensen H. Penicillin in acute otitis media: a double-blind placebo-controlled trial. *Clinical Otolaryngology* 1981;**6**:5–13.
Thomsen J, Meistrup-Larsen KI, Sorensen H, Larsen PK, Mygind N. Penicillin and acute otitis: short and long term results. *Annals of Otology, Rhinology and Laryngology, Supplement* 1980;**89**:271–4.

Neumark 2007 *{published data only}*
Neumark T, Molstad S, Rosen C, Persson L, Torngren A, Brudin L, et al.Evaluation of phenoxymethylpenicillin treatment of acute otitis media in children aged 2-16. *Scandinavian Journal of Primary Health Care* 2007;**25**: 166–71.

Spiro 2006 *{published data only}*
Spiro DM, Tay K, Arnold DH, Dziura J, Baker M, Shapiro ED. Wait-and-see prescription for the treatment of acute otitis media. *JAMA* 2006;**296**(10):1235–41.

Tähtinen 2011 *{published data only}*
Tähtinen PA, Laine MK, Huovinen P, Jalava J, Ruuskanen O, Ruohola A. A placebo-controlled trial of antimicrobial treatment for acute otitis media. *New England Journal of Medicine* 2011;**364**(2):116–26.

Thalin 1985 *{published data only}*
Thalin A, Densert O, Larsson A, Lyden E, Ripa T. Is penicillin necessary in the treatment of acute otitis media? . Proceedings of the International Conference on Acute and Secretory Otitis Media 1985, Jerusalem. Amsterdam: Kugler Publications, 1985:441–6.

vanBuchem 1981a *{published data only}*
van Buchem FL, Dunk JHM, van't Hof MA. Therapy of acute otitis media: myringotomy, antibiotics or neither? A double-blind study in children. *Lancet* 1981;**2**:883–7.

vanBuchem 1981b *{published data only}*
van Buchem FL, Dunk JHM, van't Hof MA. Therapy of acute otitis media: myringotomy, antibiotics or neither? A double-blind study in children. *Lancet* 1981;**2**:883–7.

References to studies excluded from this review

Arguedas 2011 *{published data only}*
Arguedas A, Soley C, Kamicker BJ, Jorgensen DM. Single-dose extended-release azithromycin versus a 10-day regimen of amoxicillin/clavulanate for the treatment of children with acute otitis media. *International Journal of Infectious Diseases* 2011;**15**(4):e240–8.

Casey 2012 *{published data only}*
Casey JR, Block SL, Hedrick J, Almudevar A, Pichichero ME. Comparison of amoxicillin/clavulanic acid high dose with cefdinir in the treatment of acute otitis media. *Drugs* 2012;**72**:1991–7.

Chaput 1982 *{published data only}*
Chaput de Saintonge DM, Levine DF, Temple Savage IT, Burgess GW, Sharp J, Mayhew SR, et al.Trial of three-day and ten-day courses of amoxycillin in otitis media. *BMJ Clinical Research Edition* 1982;**284**(6322):1078–81.

Engelhard 1989 *{published data only}*
Engelhard D, Strauss N, Jorczak-Sarni L, Cohen D, Sacjs TG, Shapiro M. Randomised study of myringotomy, amoxycillin/clavulanate, or both for acute otitis media in infants. *Lancet* 1989;**2**(8655):141–3.

Liu 2011 *{published data only}*
Liu P, Fang AF, LaBadie RR, Crownover PH, Arguedas AG. Comparison of azithromycin pharmacokinetics following single oral doses of extended-release and immediate-release formulations in children with acute otitis media. *Antimicrobial Agents and Chemotherapy* 2011;**55**(11): 5022–6.

Ostfeld 1987 *{published data only}*
Ostfeld E, Segal J, Kaufstein M, Gelernter I. Management of acute otitis media without primary administration of systemic antimicrobial agents. Recent advances in otitis media. Proceedings of the Fourth International Symposium. Toronto: BC Decker, 1987:235–9.

Rudberg 1954 *{published data only}*
Rudberg RD. Acute otitis media: comparative therapeutic results of sulphonamide and penicillin administered in various forms. *Acta Otolaryngology* 1954;**113**(Suppl):1–79.

Ruohola 2003 *{published data only}*
Ruohola A, Heikkinen T, Meurman O, Puhakka T, Lindblad N, Ruuskanen O. Antibiotic treatment of acute otorrhea through tympanostomy tube: randomized double-blind placebo-controlled study with daily follow-up. *Pediatrics* 2003;**111**(5):1061–7.

Sarrell 2003 *{published data only}*
Sarrell EM, Cohen HA, Kahan E. Naturopathic treatment for ear pain in children. *Pediatrics* 2003;**111**(5):574–9.

Tähtinen 2012 *{published data only}*
Tähtinen PA, Laine MK, Ruuskanen O, Ruohola A. Delayed versus immediate antimicrobial treatment for acute

otitis media. *Pediatric Infectious Disease Journal* 2012:[Epub ahead of print].

vanBuchem 1985 *{published data only}*

van Buchem F, Peeters M, Van' t Hof M. Acute otitis media: a new treatment strategy. *BMJ* 1985;**290**:1033–7.

Additional references

AAP 2004

American Academy of Pediatrics, American Academy of Family Physicians. Clinical practice guidelines: diagnosis and management of acute otitis media. *Pediatrics* 2004;**113**: 1451–65.

Akkerman 2005

Akkerman AE, Kuyvenhoven MM, van der Wouden JC, Verhij TJM. Analysis of under-and overprescribing of antibiotics in acute otitis media in general practice. *Journal of Antimicrobial Chemotherapy* 2005;**56**:569–74.

Arnold 2005

Arnold SR, Straus SE. Interventions to improve antibiotic prescribing in ambulatory care. *Cochrane Database of Systematic Reviews* 2005, Issue 4. [DOI: 10.1002/14651858.CD003539]

Arola 1990

Arola M, Ruuskanen O, Ziegler T, Mertsola J, Näntö-Salonen K, Putto-Laurila A, et al.Clinical role of respiratory virus infection in acute otitis media. *Pediatrics* 1990;**86**: 848–55.

Barkai 2009

Barkai G, Leibovitz E, Givon-Lavi N, Dagan R. Potential contribution by nontypable Haemophilus influenzae in protracted and recurrent acute otitis media. *Pediatric Infectious Disease Journal* 2009;**28**:466–71.

Berman 1995

Berman S. Otitis media in developing countries. *Pediatrics* 1995;**96**:126–31.

Cates 1999

Cates C. An evidence based approach to reducing antibiotic use in children with acute otitis media: controlled before and after the study. *BMJ* 1999;**318**:715–6. [: The handout is available at http://www.cates.cwc.net/]

Chao 2008

Chao JH, Kunkov S, Reyes LB, Lichten S, Crain EF. Comparison of two approaches to observation therapy for acute otitis media in the emergency department. *Pediatrics* 2008;**121**:31352–e6.

Chonmaitree 1992

Chonmaitree T, Owen MJ, Patel JA, Hedgpeth D, Horlick D, Howie VM. Effect of viral respiratory tract infection on outcome of acute otitis media. *Journal of Pediatrics* 1992; **120**:856–62.

Dickersin 1994

Dickersin K, Scherer R, Lefebvre C. Identifying relevant studies for systematic reviews. *BMJ* 1994;**309**(6964): 1286–91.

Froom 2001

Froom J, Culpepper L, Green LA, de Melker RA, Grob P, Heeren T, et al.A cross-national study of acute otitis media: risk factors, severity, and treatment at initial visit. Report from the International Primary Care Network (IPCN) and the Ambulatory Sentinel Practice Network (ASPN). *Journal of the American Board of Family Practice* 2001;**14**:406–17.

Gates 2002

Gates GA, Klein JO, Lim DJ, Mogi G, Ogra PL, Pararella MM, et al.Recent advances in otitis media, 1: definitions, terminology, and classification of otitis media. *Annals of Otology, Rhinology and Laryngology* 2002;**111**:8–18.

Higgins 2011

Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Klein 1989

Klein JO. Epidemiology of otitis media. *Pediatic Infectious Disease Journal* 1989;**8**(Suppl 1):89.

Koopman 2008

Koopman L, Hoes AW, Glasziou PP, Appelman CL, Burke P, McCormick DP, et al.Antibiotic therapy to prevent the development of asymptomatic middle ear effusion in children with acute otitis media. *Archives of Otolaryngology - Head and Neck Surgery* 2008;**134**(2):128–32.

Kozyrskyj 2010

Kozyrskyj A, Klassen TP, Moffatt M, Harvey K. Short-course antibiotics for acute otitis media. *Cochrane Database of Systematic Reviews* 2010, Issue 9. [DOI: 10.1002/14651858.CD001095]

Lefebvre 2011

Lefebvre C, Manheimer E, Glanville J. Chapter 6: Searching for studies. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Little 2006

Little P, Moore M, Warner G, Dunleavy J, Williamson I. Longer term outcomes from a randomised trial of prescribing strategies in otitis media. *British Journal of General Practice* 2006;**56**:176–82.

McCormick 2007

McCormick DP, Chandler SM, Chonmaitree T. Laterality of acute otitis media: different clinical and microbiologic characteristics. *Pediatric Infectious Disease Journal* 2007;**26**: 583–8.

Rosenfeld 1994

Rosenfeld RM, Vertrees JE, Carr J, Cipolle RJ, Uden DL, Giebink GS, et al.Clinical efficacy of antimicrobial drugs for acute otitis media: meta-analysis of 5400 children from thirty-three randomized trials. *Journal of Pediatrics* 1994; **124**:355–67.

Rothman 2003
Rothman R, Owens T, Simel D. Does this child have acute otitis media?. *JAMA* 2003;**290**(12):1633–40.

Rovers 2006
Rovers MM, Glasziou P, Appelman CL, Burke P, McCormick DP, Damoiseaux RA, et al.Antibiotics for acute otitis media: a meta-analysis with individual patient data. *Lancet* 2006;**368**:1429–35.

Spurling 2010
Spurling GKP, Del Mar CB, Dooley L, Foxlee R. Delayed antibiotics for respiratory infections. *Cochrane Database of Systematic Reviews* 2010, Issue 1. [DOI: 10.1002/14651858.CD004417.pub3]

Stool 1989
Stool SE, Field MJ. The impact of otitis media. *Pediatic Infectious Disease Journal* 1989;**8**(Suppl 1):11–4.

Teele 1989
Teele DW, Klein JO, Rosner B. Epidemiology of otitis media during first seven years of life in children in greater Boston: a prospective cohort study. *Journal of Infectious Diseases* 1989;**160**:83–94.

References to other published versions of this review

Glasziou 1997
Glasziou PP, Hayem M, Del Mar C B. Treatments for acute otitis media in children: antibiotic versus placebo. *Cochrane Database of Systematic Reviews* 1997, Issue 1. [DOI: 10.1002/14651858.CD000219]

Glasziou 1999
Glasziou PP, Hayem M, Del Mar CB. Antibiotics versus placebo for acute otitis media in children. *Cochrane Database of Systematic Reviews* 1999, Issue 3. [DOI: 10.1002/14651858.CD000219.pub2]

Glasziou 2005
Glasziou PP, Del Mar CB, Sanders SL, Hayem M. Antibiotics for acute otitis media in children. *Cochrane Database of Systematic Reviews* 2005, Issue 1. [DOI: 10.1002/14651858.CD000219.pub2]

Sanders 2009
Sanders SL, Glasziou PP, Del Mar CB, Rovers MM. Antibiotics for acute otitis media in children. *Cochrane Database of Systematic Reviews* 2009, Issue 2. [DOI: 10.1002/14651858.CD000219.pub2]

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Appelman 1991

Methods	**Randomised -** yes, computer-generated random numbers **Concealment of allocation -** adequate **Double-blind -** yes, blinding procedure not described **Intention-to-treat (ITT) -** unclear **Loss to follow-up -** described **Design -** parallel
Participants	**N -** 126 children (N = 121 children included in analysis) **Age -** between 6 months and 12 years **Setting -** general practice and secondary care in the Netherlands; confirmation of diagnosis and randomisation were done by otorhinolaryngologists **Inclusion criteria -** recurrence of acute otitis media (AOM) characterised by a (sub) acute onset, otalgia and otoscopic signs of middle-ear infection within 4 weeks to 12 months of the previous attack **Exclusion criteria -** antibiotic treatment < 4 weeks prior to randomisation, previous participation in this study, contraindication for penicillin, serious concurrent disease that necessitated antibiotic treatment **Baseline characteristics -** balanced
Interventions	**Tx -** amoxicillin/clavulanate (weight tailored dose) for 7 days; N = 70 (N = 67 included in analysis) **C -** matching placebo for 7 days; N = 56 (N = 54 included in analysis) **Use of additional medication -** each child was given analgesics (paracetamol) as long as earache was present and decongestive nose drops for 1 week
Outcomes	**Primary outcome -** treatment failure (i.e. presence of otalgia or fever > 38 °C or both at 3 days) Assessment by (blinded) general practitioner at 3 days on the presence or absence of fever (> 38 °C) and otalgia and 14 days on the presence or otorrhoea Assessment by otorhinolaryngologist at 1 month of otoscopy, tympanometry and in children > 3 years of age an audiogram
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers
Allocation concealment (selection bias)	Low risk	Treatment allocated by otolaryngologist (independent to trial personnel); treatment code placed in sealed envelopes

Appelman 1991 (*Continued*)

Other bias	Unclear risk	ITT analysis - unclear, baseline characteristics - balanced
Blinding of participants and personnel (performance bias)	Unclear risk	Identical taste and appearance of co-amoxiclav and placebo not described
Incomplete outcome data (attrition bias)	Low risk	Loss to follow-up - treatment: N = 3 (4%) and placebo: N = 2 (4%) due to loss of their registration forms

Burke 1991

Methods	**Randomised -** yes, computer-generated random numbers **Concealment of allocation -** adequate **Double-blind -** yes **Intention-to-treat (ITT) -** yes **Loss to follow-up -** not described **Design -** parallel
Participants	**N -** 232 children **Age -** between 3 and 10 years **Setting -** general practice; 48 general practitioners in 17 general practices in Southampton, Bristol and Portsmouth (UK) **Inclusion criteria -** acute earache and at least 1 abnormal eardrum **Exclusion criteria -** antibiotic treatment or acute otitis media (AOM) < 2 weeks prior to randomisation, strong indication for antibiotic treatment according to general practitioner, contraindication for amoxicillin, serious chronic conditions **Baseline characteristics -** slight imbalance in gender (boys treated with antibiotics versus boys treated with placebo = 52% versus 42%) and figure 1 appears to demonstrate that fewer children were crying at baseline (0 hours) in the amoxicillin arm as compared to the placebo arm suggesting a failure of randomisation
Interventions	**Tx -** amoxicillin 250 mg 3 times daily for 7 days; N = 114 (N = 114 included in analysis for short-term outcome) **C -** matching placebo 3 times daily for 7 days; N = 118 (N = 118 included in analysis for short-term outcome) **Use of additional medication -** analgesics (paracetamol 120 mg/5 mL) for pain as needed
Outcomes	**Main outcomes** were divided into short-term, middle-term and long-term: **Short-term -** (a) duration of symptoms; (b) use of analgesics (assessed by weighing bottles); (c) clinical signs at 1 week; (d) incidence of complications; (e) treatment failure (i.e. second-line antibiotics were required) **Middle-term -** (a) tympanometry findings at 1 and 3 months **Long-term -** (b) number of AOM episodes in 12 months; (b) number of specialist referrals Home visits by researcher at day 1, days 4 to 6 and general practitioner visit at day 7 Symptom diary kept by parents for 21 days

Burke 1991 (*Continued*)

Notes	It is not clear whether the "discharging ears" in Table 1 should be included as perforations, we now included the number of perforations as summarised in Table 2 in our analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers
Allocation concealment (selection bias)	Low risk	Randomisation was carried out independently of the investigators; randomisation code was kept sealed and was unknown to any of the participants in the study
Other bias	Unclear risk	ITT analysis - yes; baseline characteristics - imbalance for gender and crying
Blinding of participants and personnel (performance bias)	Low risk	Each bottle was identified only by number
Incomplete outcome data (attrition bias)	Unclear risk	Loss to follow-up - not described; all randomised patients included in short-outcome analysis

Damoiseaux 2000

Methods	**Randomised -** yes, computerised 2 block randomisation **Concealment of allocation -** adequate **Double-blind -** yes **Intention-to-treat (ITT) -** yes **Loss to follow-up -** described **Design -** parallel
Participants	**N -** 240 children (N = 212 children included in analysis) **Age -** between 6 months and 2 years **Setting -** general practice; 53 general practitioners (GPs) in the Netherlands **Inclusion criteria -** acute otitis media (AOM) defined as infection of the middle ear of acute onset and a characteristic eardrum picture (injection along the handle of the malleus and the annulus of the tympanic membrane or a diffusely red or bulging eardrum) or acute otorrhoea. In addition 1 or more symptoms of acute infection (fever, recent earache, general malaise, recent irritability) **Exclusion criteria -** antibiotic treatment < 4 weeks prior to randomisation, contraindication for amoxicillin, comprised immunity, craniofacial abnormalities, Down's syndrome, or being entered in this study before **Baseline characteristics -** slight imbalance in the prevalence of recurrent AOM, regular attendance to a daycare centre and parenteral smoking; logistic regression was used to

Damoiseaux 2000 (*Continued*)

	adjust for these imbalances
Interventions	**Tx -** amoxicillin suspension 40 mg/kg/day 3 times daily for 10 days; N = 117 (N = 107 included in analysis for short-term outcome) **C -** matching placebo suspension for 10 days; N = 123 (N = 105 included in analysis for short-term outcome) **Use of additional medication -** all children received decongestive nose drops for 7 days; analgesics (paracetamol, children < 1 year: 120 mg suppository, > 1 year: 240 mg suppository) was allowed
Outcomes	**Primary outcome -** persistent symptoms at day 4: assessed by the doctor and defined as persistent earache, fever > 38 °C, crying, or being irritable. Additionally, prescription of another antibiotic because of clinical deterioration before the first follow-up visit was to be considered a persistent symptom **Secondary outcomes -** (a) clinical treatment failure at day 11 (i.e. persistent fever, earache, crying, being irritable, or no improvement of tympanic membrane (including perforation); (b) duration of fever, pain or crying; (c) mean number of doses analgesics given; (d) adverse effects mentioned in diaries; (e) percentage of children with middle-ear effusion at 6 weeks (i.e. combined otoscopy and tympanometry) Follow-up visits at the GPs' clinic were scheduled at day 4 and 11; home visit at 6 weeks by the researcher collecting data of symptoms, referrals and both otoscopy and tympanometry was performed Parents were instructed to keep a symptom diary for 10 days
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computerised 2 block randomisation
Allocation concealment (selection bias)	Low risk	Randomisation was carried out independently of the investigators; randomisation code was kept in pharmacy of the University Medical Centre Utrecht
Other bias	Low risk	ITT analysis - yes, baseline characteristics - slight imbalance, logistic regression was used to adjust for imbalances in prognostic factors
Blinding of participants and personnel (performance bias)	Low risk	Placebo suspension with same taste and appearance of amoxicillin
Incomplete outcome data (attrition bias)	Unclear risk	Loss to follow-up/exclusion from analysis (received other antibiotics or had grommets inserted) - treatment: N = 10 (9%) and

		placebo: N = 18 (15%). However, for primary analysis of symptoms at day 4 all randomised patients were included

Halsted 1968

Methods	**Randomised -** yes, pre-determined code which was unknown to physician; method of random sequence generation unclear **Concealment of allocation -** adequate **Double-blind -** yes **Intention-to-treat (ITT) -** unclear **Loss to follow-up -** described, unclear from which treatment group patients were excluded **Design -** parallel
Participants	**N -** 106 children (N = 89 children included in analysis; N = 12 children were excluded because they were not adhere to the double-blind protocol; N = 5 children lost to follow-up or excluded because of persistent fever, development of complication requiring antibiotic treatment, or if group A streptococci was cultured from middle ear) **Age -** between 2 months and 5.5 years **Setting -** secondary care: paediatric department of Cleveland (USA) **Inclusion criteria -** AOM based on otoscopic findings; most of the cases had bulging membrane with loss of normal light reflex and landmarks, in a few the eardrum was only diffusely red **Exclusion criteria -** antibiotic treatment < 10 days prior to randomisation, associated bacterial infection requiring antibiotic treatment, rupture of tympanic membrane, contraindication for study drugs **Baseline characteristics -** not described
Interventions	**Tx 1 -** ampicillin 100 mg/kg/day 4 daily for 10 days; N = ? (N = 30 included in analysis) **Tx 2 -** pheneticillin 30 mg/kg/day 4 daily and sulfisoxazole 150 mg/kg/day 4 daily for 10 days; N = ? (N = 32 included in analysis) **C -** placebo for 10 days; N = ? (N = 27 included in analysis) **Use of additional medication -** phenylephrine nose drops and aspirin for children over 6 months was prescribed as necessary; no other medications were employed
Outcomes	**Primary outcome -** early improvement defined as defervescence and decrease of symptoms at 24 to 72 hours **Secondary outcomes -** (a) late improvement defined as resolution of symptoms and normal tympanic membrane at 14 to 18 days, (b) bacteriological cultures
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Halsted 1968 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Pre-determined code which was unknown to physician; method of random sequence generation unclear
Allocation concealment (selection bias)	Unclear risk	Method not described
Other bias	Unclear risk	ITT analysis - unclear, baseline characteristics - not described
Blinding of participants and personnel (performance bias)	Unclear risk	Identical taste and appearance of antibiotics and placebo not described
Incomplete outcome data (attrition bias)	Unclear risk	Reasons described, unclear from which treatment group patients were excluded

Hoberman 2011

Methods	**Randomised -** yes, stratified block randomisation with computer-generated randomisation lists **Concealment of allocation -** adequate **Double-blind -** yes **Intention-to-treat (ITT) -** yes **Loss to follow-up -** described **Design -** parallel
Participants	**N -** 291 (N = 291 included in analysis) **Age -** between 6 months and 2 years **Setting -** secondary care; children's hospital of Pittsburgh and a private paediatric clinic in Kittanning (USA) **Inclusion criteria -** children needed to have received at least 2 doses of pneumococcal conjugate vaccine and to have acute otitis media (AOM) as defined on the basis of 3 criteria: (a) the onset (i.e. within the preceding 48 hours) of symptoms that parents rated with a score of at least 3 on the acute otitis media - severity of symptoms (AOM-SOS) scale (on which scores range from 0 to 14, with higher scores indicating greater severity of symptoms), (b) the presence of middle-ear effusion and (c) moderate or marked bulging of the tympanic membrane or slight bulging accompanied by either otalgia or marked erythema of the membrane All the study clinicians were otoscopists who had successfully completed an otoscopic validation programme **Exclusion criteria -** antibiotic treatment < 96 hours prior to randomisation, concomitant acute illness (e.g. pneumonia) or a chronic illness (e.g. cystic fibrosis), contraindication to amoxicillin, presence of otalgia for more than 48 hours, perforation of the tympanic membrane **Baseline characteristics -** balanced
Interventions	**Tx -** amoxicillin-clavulanate 90-6.4 mg/kg daily in 2 doses for 10 days; N = 144 (N = 139 were assessed at day 4 to 5) **C -** matching placebo in 2 doses for 10 days; N = 147 (N = 142 were assessed at day 4

	to 5) **Use of additional medication -** acetaminophen (paracetamol) as needed for symptom relief At each visit children were categorised as having met the criteria for either clinical success or clinical failure Children who met the criteria for clinical failure were treated with a standardised 10-day regimen of orally administered amoxicillin (90 mg/kg daily) and cefixime (8 mg/kg daily)
Outcomes	**Primary outcomes -** (a) time to resolution of symptoms (i.e. time to the first recording of an AOM-SOS score of 0 or 1 and the time to the second of 2 successive recordings of that score; (b) symptom burden over time (i.e. mean AOM-SOS score over time each day for the first 7 days of follow-up and groups' weighted mean scores for that period) **Secondary outcomes -** (a) clinical failure at day 4 to 5; (b) clinical failure at day 10 to 12; (c) use of acetaminophen (paracetamol); (d) occurrence of adverse events; (e) nasopharyngeal colonisation rates; (f) use of healthcare resources (g) relapses Clinical failure was defined at or before the day 4 to 5 visit as either a lack of substantial improvement in symptoms, a worsening of signs on otoscopic examination, or both and at the day 10 to 12 visit as the failure to achieve complete or nearly complete resolutions of symptoms and otoscopic signs, without regard to the persistence of resolution of middle-ear effusion. Once a child had met the criteria for clinical failure, he or she remained in that category for the analysis Daily symptoms were assessed with the use of a structured interview of 1 of the child's parents until the first follow-up visit; visits were scheduled at day 4 or 5, day 10 to 12 (end of treatment) and at day 21 to 25 Patients were asked to complete a diary twice a day for 3 days and once a day thereafter
Notes	This study did not report pain data that could be used for the review comparing antibiotics with placebo

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Stratified block randomisation with computer-generated randomisation lists
Allocation concealment (selection bias)	Low risk	A pharmacist (independent to trial team) provided masked study medication bottles with amoxicillin/clavulanate or placebo
Other bias	Low risk	ITT analysis - yes, baseline characteristics - balanced
Blinding of participants and personnel (performance bias)	Low risk	Placebo with same taste and appearance of amoxicillin-clavulanate

Incomplete outcome data (attrition bias)	Low risk	Children not assessed at day 4 to 5 - treatment: N = 5 (3%) and placebo: N = 5 (3%) . All randomised patients included in analysis

Howie 1972

Methods	**Randomised -** yes, method of randomisation not described **Concealment of allocation -** adequate **Double-blind -** yes **Intention-to-treat (ITT) -** unclear **Loss to follow-up -** not described **Design -** parallel
Participants	**N -** 280 children **Age -** 2.5 years or younger **Setting -** secondary care: general paediatric practice in Huntsville (USA) **Inclusion criteria -** acute otitis media (AOM) as clinically diagnosed by the participating paediatricians **Exclusion criteria -** if researchers felt that parents would not accept diagnostic aspiration, when condition of the patient required immediate antibiotic treatment **Baseline characteristics -** not described
Interventions	**Tx 1 -** erythromycin estolate 125 mg/5 mL - triple sulphonamide suspension 0.5 g/5 mL; N = 80 **Tx 2 -** ampicillin 250 mg/5 mL; N = 36 **Tx 3 -** triple sulphonamide suspension 0.5 g/5 mL; N = 23 **Tx 4 -** erythromycin estolate 125 mg/5 mL; N = 25 **C 1 -** placebo - equal parts acetaminophen (paracetamol) and chlorpheniramine maleate syrup; N = 33 **C 2 -** placebo - 4 parts Kaopectate and 1 part acetaminophen (paracetamol, Tylenol) plus food colouring; N = 83 **Use of additional medication -** all children received decongestive nose drops for 7 days; analgesics (paracetamol, children < 1 year: 120 mg suppository, > 1 year: 240 mg suppository) was allowed
Outcomes	**Primary outcomes -** (a) presence or absence of exudate while on medication; (b) bacteriological findings of the exudate when present; no patient-relevant outcomes were described At baseline and before treatment was started, the middle-ear exudate was aspirated. The decision whether to collect exudate on the first repeat visit was made with no knowledge of the drug regimen to which the patient had been assigned
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Howie 1972 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Method of randomisation not described
Allocation concealment (selection bias)	Low risk	Randomisation was performed by a collaborating pharmacist
Other bias	Unclear risk	ITT analysis - unclear, baseline characteristics - not described
Blinding of participants and personnel (performance bias)	Unclear risk	Identical taste and appearance of co-amoxiclav and placebo not described
Incomplete outcome data (attrition bias)	Unclear risk	Loss to follow-up - not described

Kaleida 1991

Methods	**Randomised -** yes, stratified randomisation, method of randomisation not described **Concealment of allocation -** unclear, method not described **Double-blind -** yes, blinding procedure not described **Intention-to-treat (ITT) -** yes **Loss to follow-up -** not described **Design -** parallel
Participants	**N -** 536 children (representing 1049 non-severe acute otitis media (AOM) episodes; 980 non-severe AOM episodes included for primary analysis) **Age -** between 7 months and 12 years **Setting -** secondary care: children's hospital and a private paediatric practice in Pittsburgh (USA) **Inclusion criteria -** AOM based on presence of middle-ear effusion, as determined otoscopically, in association with specified symptoms of acute middle-ear infection (fever, otalgia or irritability), or signs of acute infection (erythema or white opacification, or both, accompanied by fullness or bulging and impaired mobility), or both **Exclusion criteria -** children who recently received antibiotics, who had potential complicating or confounding conditions (e.g. eardrum perforation, asthma, or chronic sinusitis) **Baseline characteristics -** balanced
Interventions	Children were enrolled for a 1-year period. At entry each child was assigned randomly to a treatment regimen that specified consistent treatments for episodes of non-severe and severe AOM based on severity of otalgia and the presence of fever (> 39 °C orally or > 39.5 °C rectally within the 24-hour period before presentation) **Non-severe AOM episodes** were treated with: Tx - amoxicillin 40 mg/kg/day 3 times daily for 14 days; N = 522 (N = 488 included in primary analysis) C - placebo for 14 days; N = 527 (N = 492 included in primary analysis) **Severe AOM episodes** in children aged < 2 years were treated with: Tx 1 - amoxicillin 40 mg/kg/day 3 times daily for 14 days Tx 2 - amoxicillin 40 mg/kg/day 3 times daily for 14 days and myringotomy

Kaleida 1991 (*Continued*)

	Severe AOM episodes in children aged ≥ 2 years were treated with: Tx 1 - amoxicillin 40 mg/kg/day 3 times daily for 14 days Tx 2 - amoxicillin 40 mg/kg/day 3 times daily for 14 days and myringotomy Tx 3 - placebo and myringotomy
Outcomes	**Primary outcome -** initial treatment failure: in non-severe episodes this was the case when either otalgia, fever, or both was present more than 24 hours after treatment was initiated and when 48 hours or more after initial treatment was initiated the child's temperature reached 38 °C orally or 38.5 °C rectally or an otalgia score of ≥ 6 was present **Secondary outcomes -** (a) recurrent AOM defined as the development of AOM 15 days or more after the initiation of treatment for a preceding episode (b) new episodes of otitis media with effusion defined by otoscopy and tympanometry findings After initial visits, children were followed up by telephone to identify those with persistent symptoms and children younger than 2 years of age were re-examined within 48 to 72 hours Follow-up visits were scheduled routinely after 2 and 6 weeks after initial treatment and monthly thereafter
Notes	We included only the non-severe AOM episodes in this review (N = 1049 of which 980 were included for primary analysis); children experiencing non-severe AOM episodes were randomly allocated to either antibiotics or placebo

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not described
Allocation concealment (selection bias)	Unclear risk	Method not described
Other bias	Low risk	ITT analysis - yes, baseline characteristics - balanced
Blinding of participants and personnel (performance bias)	Unclear risk	Identical taste and appearance of amoxicillin and placebo not described
Incomplete outcome data (attrition bias)	Unclear risk	Follow-up/exclusion of non-severe episodes for short-term outcome - treatment: N = 34 (7%) and placebo: N = 35 (7%). Reasons not described

Laxdal 1970

Methods	**Randomised -** yes, method of randomisation not described **Concealment of allocation -** unclear; method not described **Double-blind -** no; open-label study, investigators not blinded **Intention-to-treat (ITT) -** unclear **Loss to follow-up -** not described **Design -** parallel
Participants	**N -** 142 children **Age -** between 0 to 15 years **Setting -** secondary care (private paediatric clinic) in Saskatoon (Canada) **Inclusion criteria -** at least 1 eardrum had to show redness and loss of landmarks **Exclusion criteria -** predominant respiratory symptoms, if allergy appeared to be a significant factor or if rupture of the eardrum had occurred **Baseline characteristics -** not described
Interventions	**Tx 1 -** penicillin G 250 mg/m^2/day 4 times daily (approximately 33 mg/kg/day) for at least 7 days; N = 45 **Tx 2 -** ampicillin 250 mg/m^2/day 4 times daily (approximately 33 mg/kg/day) for at least 7 days; N = 49 **C -** symptomatic therapy (Auralgan ear drops, acetylsalicylic acid, decongestive nose drops); N = 48 **Use of additional medication -** children in treatment groups also received symptomatic therapy as required
Outcomes	**Primary outcomes -** (a) treatment failure (i.e. either deterioration or no improvement observed at day 7) (b) relapses Results were evaluated at 7 days, except in cases where the ear inflammation was severe and the child appeared sufficiently ill (toxic) to warrant further examination 24 to 48 hours after treatment initiation Children in the control group were subjected to very close scrutiny, especially during the first 48 hours and particularly when severe involvement was evident (detection bias)
Notes	Open-label trial comparing immediate antibiotics (penicillin G and ampicillin) versus expectant observation It was unclear whether otalgia played an important role in the definition of treatment failure Data on relapses: N = 126 included in analysis, no crude numbers for separate treatment groups provided

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not described
Allocation concealment (selection bias)	Unclear risk	Not described

Laxdal 1970 (*Continued*)

Other bias	High risk	ITT analysis - unclear, baseline characteristics - not described, detection bias due to different follow-up strategies between treatment groups
Blinding of participants and personnel (performance bias)	Unclear risk	Open-label trial, outcome assessment not blinded
Incomplete outcome data (attrition bias)	Unclear risk	Loss to follow-up - not described for short-term outcome. Loss to follow-up for long-term outcome (acute otitis media (AOM) relapses) - N = 16 (11%), no crude numbers of separate treatment groups provided

Le Saux 2005

Methods	**Randomised -** yes, computer-generated randomisation sequence **Concealment of allocation -** adequate **Double-blind -** yes **Intention-to-treat (ITT) -** yes **Loss to follow-up -** described **Design -** parallel
Participants	**N -** 531 children (N = 512 children included in analysis; N = 19 were post-hoc excluded due to inappropriate randomisation (N = 4) or alternative clinical diagnosis (N = 15)) **Age -** between 6 months and 5 years **Setting -** secondary care: emergency department in Ottawa (Canada) **Inclusion criteria -** new onset (< 4 days) of symptoms referable to the upper respiratory tract and either ear pain or fever (> 38 °C). In addition, all patients had to have evidence of middle-ear effusion, defined by ≥ 2 of the following signs: opacity, impaired mobility on the basis of pneumatic otoscopy and redness or bulging (or both) of the tympanic membrane **Exclusion criteria -** antibiotic treatment < 2 weeks prior to randomisation, contraindication to amoxicillin or penicillin or sensitivity to ibuprofen or aspirin, presence of otorrhoea, co-morbid disease such as sinusitis or pneumonia, prior middle-ear surgery, placement of a ventilation tube, history of recurrent acute otitis media (more than 4 episodes in 12 months), compromised immunity, craniofacial abnormalities, or any chronic or genetic disorder **Baseline characteristics -** balanced
Interventions	**Tx -** amoxicillin suspension (60 mg/kg) 3 times daily for 10 days; N = 258 (N = 253 included in analysis for day 3) **C -** matching placebo for 10 days; N = 254 (N = 246 included in analysis for day 3) **Use of additional medication -** parents were given a 5-day supply of antipyretic and analgesic medication in the form of ibuprofen suspension as required for pain or fever and a 48-hour supply of codeine elixir to be given as required for pain and fever

Outcomes	**Primary outcome -** clinical resolution of symptoms, defined as absence of receipt of an antimicrobial (other than amoxicillin in the treatment group) at any time during the 14-day period. The initiation of antimicrobial therapy was based on persistence or worsening of symptoms, fever or irritability associated with otoscopic signs of unresolving AOM, or development of symptoms indicative for mastoiditis or invasive disease **Secondary outcomes -** (a) presence of symptoms (i.e. fever, pain, irritability, vomiting, activity level) on days 1, 2 and 3; (b) number of analgesic doses, codeine doses on days 1, 2 and 3; (c) occurrence of any rash or diarrhoea in the 14 days after randomisation; (d) presence of middle-ear effusion assessed by tympanometry at 1 and 3 months after diagnosis The parents were contacted on days 1, 2 and 3 after randomisation and once between day 10 and day 14 for administration of a standard questionnaire. If the parents or research assistant felt that the symptoms were not improving or were worsening, a medical reassessment was advised and the child was seen by a physician in the emergency department or clinic or by the paediatrician The child was clinically assessed at 1 month and 3 months after randomisation to determine the number of subsequent episodes of acute otitis media (AOM) and to undergo tympanometry
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation sequence stratified by study centre and age using random-permuted blocks of sizes 4 and 6
Allocation concealment (selection bias)	Low risk	Randomisation sequence was kept under secure conditions and was accessible only to the trial pharmacist
Other bias	Low risk	ITT analysis - yes, baseline characteristics - balanced
Blinding of participants and personnel (performance bias)	Low risk	Placebo was similar with amoxicillin with regard to appearance and taste and were dispensed in identical opaque bottles which were numbered sequentially
Incomplete outcome data (attrition bias)	Low risk	Loss to follow-up at day 3 - treatment: N = 5 (2%) and placebo: N = 8 (3%)

Little 2001

Methods	**Randomised -** yes, method of randomisation not described **Concealment of allocation -** adequate **Double-blind -** no; open-label study, investigators not blinded **Intention-to-treat (ITT) -** yes **Loss to follow-up -** described **Design -** parallel
Participants	**N -** 315 children (N = 285 children included in analysis) **Age -** between 6 months and 10 years **Setting -** general practice; 42 general practitioners in 3 health authorities in south-west England **Inclusion criteria -** acute otalgia and otoscopic evidence of acute inflammation of the eardrum (dullness or cloudiness with erythema, bulging or perforation). When children were too young for otalgia to be specifically documented from their history (under 3 years old) then otoscopic evidence alone was a sufficient entry criterion **Exclusion criteria -** otoscopic appearances consistent with crying or a fever alone (pink drum alone), appearances and history more suggestive of otitis media with effusion and chronic suppurative otitis media, serious chronic disease (such as cystic fibrosis, valvular heart disease), use of antibiotics < 2 weeks prior to randomisation, previous complications (septic complications, hearing impairment) and if the child was unwell to be left to wait and see (e.g. high fever, floppy, drowsy, not responding to antipyretics) **Baseline characteristics -** balanced
Interventions	**Tx -** immediate treatment with antibiotics: amoxicillin syrup 125 mg/5 mL 3 times daily for 7 days (children who were allergic to amoxicillin received erythromycin 125 mg/5 mL 4 times daily; N = 151 (N = 135 included in analysis) **C -** similar antibiotics were prescribed but parents were asked to wait for 72 hours before considering using the prescription. Parents were instructed that if their child still had substantial otalgia or fever after 72 hours, had discharge for > 10 days or was not starting to get better then they should collect the antibiotic prescription that was left at practice; N = 164 (N = 150 included in analysis) **Use of additional medication -** for both groups doctors emphasised the importance of paracetamol in full doses for relief of pain and fever
Outcomes	**Primary outcomes -** (a) duration of symptoms (i.e. earache, ear discharge, night disturbance, crying); (b) daily pain score; (c) episodes of distress; (d) spoons of paracetamol used; (e) use of antibiotics Doctors were asked to provide information on days of illness, physical signs and antibiotic prescribing; parents were asked to complete a daily symptom diary
Notes	Open-label trial comparing immediate versus delayed antibiotic prescription (prescription provided but advised to fill only if symptoms did not improve or worsened)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not described

Little 2001 (*Continued*)

Allocation concealment (selection bias)	Low risk	Sealed numbered opaque envelopes
Other bias	Low risk	ITT analysis - yes, baseline characteristics - balanced
Blinding of participants and personnel (performance bias)	Unclear risk	Open-label trial, outcome assessment not blinded
Incomplete outcome data (attrition bias)	Low risk	Loss to follow-up/exclusion from analysis (intervention ineffective, did not use antibiotics or did not delay) - treatment: N = 16 (12%) and placebo: N = 14 (9%); comparison of the baseline information of the 3 types of responders (those who provided diaries, those who gave information by telephone and those from whom no diary information could be collected) revealed no evidence of significant bias between treatment groups or between patients by age or severity of symptoms

McCormick 2005

Methods	**Randomised -** yes, computer-generated randomisation sequence **Concealment of allocation -** unclear; method not described **Double-blind -** no, open-label trial, investigators blinded, parents not blinded **Intention-to-treat (ITT) -** yes **Loss to follow-up -** described **Design -** parallel
Participants	**N -** 223 children (N = 218 children included in analysis at day 12) **Age -** between 6 months and 12 years **Setting -** secondary care: paediatric clinic of University of Texas Medical Branch (USA) **Inclusion criteria -** children were required to have (a) symptoms of ear infection; (b) otoscopic evidence of acute otitis media (AOM), including middle-ear effusion; (c) non-severe AOM **Exclusion criteria -** co-morbidity requiring antibiotic treatment, anatomic defect of ear or nasopharynx, allergy to study medication, immunologic deficiency, major medical condition and/or indwelling ventilation tube or draining otitis in the affected ear(s) **Baseline characteristics -** balanced
Interventions	**Tx -** immediate treatment with antibiotics: oral amoxicillin 90 mg/kg/day twice daily for 10 days; N = 112 (N = 110 included in analysis at day 12) **C -** expectant observation: no immediate antibiotics; N = 111 (N = 108 included in analysis at day 12) Children in the control group with AOM failure or recurrence received oral amoxicillin 90 mg/kg/day; children in Tx group with AOM failure or recurrence received amoxicillin-clavulanate (90 mg/kg/day of amoxicillin component)

	Use of additional medication - all parents received saline nose drops and/or cerumen-removal drops (if needed), ibuprofen and over-the-counter decongestant/antihistamine to be given as needed
Outcomes	**Primary outcomes -** (a) parent satisfaction with AOM care; (b) resolution of AOM symptoms after treatment, including number of doses of symptom medication given; (c) AOM failure (days 0 to 12) or recurrence (days 13 to 30) defined as attending to the paediatrician clinic with acute ear symptoms, an abnormal tympanic membrane, or an AOM severity score higher than that at enrolment; (d) nasopharyngeal carriage of *Streptococcus pneumoniae* strains resistant to antibiotics **Secondary outcomes -** (a) minor adverse events caused by medication (e.g. allergy, diarrhoea and candidal infection); (b) serious AOM-related adverse events (e.g. invasive pneumococcal disease, mastoiditis, bacteraemia, meningitis, perforation of the tympanic membrane, hospitalisation and emergency ear surgery; (c) parent-child quality-of-life measures related to AOM Parents were instructed to complete a symptom diary from day 1 to 10 and a satisfaction questionnaire on day 12 and day 30; routine follow-up appointments for data collection were scheduled for day 12 and day 30. Patient-initiated visits was scheduled on request by the parents for children who seemed to not be responding to treatment
Notes	Investigator-blinded trial comparing immediate antibiotic prescribing versus expectant observation (no prescription provided)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation sequence
Allocation concealment (selection bias)	Unclear risk	Method not described
Other bias	Low risk	ITT analysis - yes, baseline characteristics - balanced
Blinding of participants and personnel (performance bias)	Unclear risk	Investigator-blinded study, parents not blinded
Incomplete outcome data (attrition bias)	Low risk	Loss to follow-up at day 12 - treatment: N = 2 (2%) and expectant observation: N = 3 (3%)

Mygind 1981

Methods	**Randomised -** yes, method of randomisation not described **Concealment of allocation -** adequate **Double-blind -** yes **Intention-to-treat (ITT) -** unclear **Loss to follow-up -** reasons described, unclear from which treatment group patients were excluded **Design -** parallel
Participants	**N -** 158 children (N = 149 included in analysis) **Age -** between 1 and 10 years **Setting -** general practice and secondary care: confirmation of diagnosis and trial recruitment were done by otorhinolaryngologists in Copenhagen (Denmark) **Inclusion criteria -** earache for 1 to 24 hours. The diagnosis was made if the child cried because of pain and if the tympanic membrane appeared to be red and inflamed **Exclusion criteria -** antibiotic treatment < 4 weeks prior to randomisation, other treatment apart from acetylsalicylic acid already commenced, secretion in the external ear, suspected chronic otitis media, treatment for secretory otitis media within last 12 months, concurrent disease (e.g. pneumonia or severe tonsillitis), suspected penicillin allergy **Baseline characteristics -** balanced
Interventions	**Tx -** penicillin 50 mg/mL 4 times daily; children aged 1 to 2 years: 10 mL daily, children between 3 and 5 years: 20 mL daily, children between 6 and 10 years: 30 mL daily for 7 days; N = ? (N = 72 included in analysis) **C -** placebo for 7 days; N = ? (N = 77 included in analysis) **Use of additional medication -** acetylsalicylic acid tablets (maximum of 50 mg/kg/day for 3 days) were supplied as the only supplementary treatment permitted
Outcomes	**Main outcomes:** (a) mean symptoms (i.e. pain, fever) scores; (b) number of analgesic tables used; (c) contralateral otitis; (d) spontaneous perforation of tympanic membrane; (e) mean number of days of otorrhoea; (f) tympanometry results at 1 week, 4 weeks and 3 months Initial visits were performed at home: otoscopy and bacterial culture from nasopharynx were performed Score cards were given to parents Follow-up visits at hospital at day 2 to 3, day 7, week 4 and week 12. If supplementary treatment was required at day 2 to 3, then myringotomy was performed. If supplementary treatment was required at day 7, then amoxicillin was given
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not described
Allocation concealment (selection bias)	Low risk	Randomisation performed by pharmaceutical company. Penicillin and placebo were

Mygind 1981 (*Continued*)

		supplied in coded bottles to study personnel
Other bias	Unclear risk	ITT analysis - unclear, baseline characteristics - balanced
Blinding of participants and personnel (performance bias)	Unclear risk	Identical taste and appearance of amoxicillin and placebo not described
Incomplete outcome data (attrition bias)	Unclear risk	Patients not included in analysis - N = 9 (6%). Reasons described, unclear from which treatment group patients were excluded

Neumark 2007

Methods	**Randomised -** yes, Internet-based random number generator **Concealment of allocation -** unclear; method not described **Double-blind -** no, open-label trial **Intention-to-treat (ITT) -** unclear **Loss to follow-up -** reasons described, unclear from which treatment group patients were excluded **Design -** parallel
Participants	**N -** 186 children (N = 179 patients were included in analysis; 7 patients were excluded due to non-compliance with protocol) **Age -** between 2 and 16 years **Setting -** general practice: 32 healthcare centres and 72 general practitioners in Sweden **Inclusion criteria -** acute otitis media (AOM) was based on direct inspection of the eardrum by pneumatic otoscope or preferably an aural microscope. Findings had to include a bulging, red eardrum displaying reduced mobility **Exclusion criteria -** perforation of the eardrum, chronic ear conditions or impaired hearing, previous adverse reactions to penicillin, concurrent disease that should be treated with antibiotics, recurrent AOM (3 or more AOM episodes during the past 6 months) , children with immunosuppressive conditions, genetic disorders and mental disease or retardation **Baseline characteristics -** balanced
Interventions	**Tx -** immediate treatment with antibiotics: phenoxymethylpenicillin 25 mg/kg twice daily for 5 days; N = 92 **C -** expectant observation: no immediate antibiotics; N = 87 The guardians received written information about how to act if the condition did not improve or got worse within 3 days after randomisation **Use of additional medication -** symptomatic treatment with paracetamol or non-steroidal anti-inflammatory drugs (NSAIDs), drugs reducing the swelling of the nasal mucosa (e.g. decongestive nose drops) and nasal steroids were allowed

Neumark 2007 (*Continued*)

Outcomes	**Primary outcomes -** (a) pain at day 0, 1, 2 and 3 to 7; (b) use of analgesics at day 0, 1, 2, 3, 4 to 7; (c) fever > 38 °C at day 0, 1, 2 and 3 to 7; (d) subjective recovery at day 14 and 3 months; (e) perforations at 3 months; (f) serous otitis media at 3 months All participants were asked to complete a symptom diary for 7 days; a nurse telephoned all participants after approximately 14 days to supplement the information in the diary and to register all acute contacts that had occurred during the first week of treatment; the final follow-up was performed after 3 months to register perforations and serous otitis media
Notes	Open-label trial comparing immediate antibiotic prescribing versus expectant observation (no prescription provided but advice on what to do if symptoms did not improve or worsened)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Internet-based random number generator
Allocation concealment (selection bias)	Unclear risk	Method not described
Other bias	Unclear risk	ITT analysis - unclear, baseline characteristics - balanced
Blinding of participants and personnel (performance bias)	Unclear risk	Open-label trial, outcome assessment not blinded
Incomplete outcome data (attrition bias)	Unclear risk	Patients not included in analysis - N = 7 (4%). Reasons described, unclear from which treatment group patients were excluded

Spiro 2006

Methods	**Randomised -** yes, computer-assisted randomisation **Concealment of allocation -** adequate **Double-blind -** no, open-label study, investigators blinded **Intention-to-treat (ITT) -** yes **Loss to follow-up -** described **Design -** parallel
Participants	**N -** 283 children (N = 265 children included in analysis at days 4 to 6) **Age -** between 6 months and 12 years **Setting -** secondary care: paediatric emergency department of Yale-New Haven Hospital in New Haven (USA) **Inclusion criteria -** the diagnosis of acute otitis media (AOM) was made at the discretion of the clinician according to the diagnostic criteria of the evidence-based guideline

	published in *Pediatrics* 2004 **Exclusion criteria -** presence of additional intercurrent bacterial infection such as pneumonia, if the patient appeared to be "toxic" as determined by the clinician, hospitalisation, immunocompromised children, antibiotic treatment < 1 week prior to randomisation, children who had either myringotomy or a perforated tympanic membrane, uncertain access to medical care (e.g. no telephone access), primary language of parents was neither English nor Spanish, previous enrolment in the study **Baseline characteristics -** balanced
Interventions	**Tx -** immediate treatment with antibiotics; N = 145 (N = 133 included in analysis at days 4 to 6) **C -** participants randomised to delayed prescription were given written and verbal instructions "not to fill the antibiotic prescription unless your child either is not better or is worse 48 hours (2 days) after today's visit"; N = 138 (N = 132 included in analysis at days 4 to 6) **Use of additional medication -** all participants received complimentary bottles of ibuprofen suspension (100 mg/5 mL) and analgesic ear drops
Outcomes	**Primary outcome -** proportion of each group that filled the prescription for an antibiotic. This was defined by whether the parent filled the prescription within 3 days of enrolment and was determined by the response to this question at the interview at day 4 to 6 **Secondary outcomes -** (a) clinical course of the illness; (b) adverse effects of medications; (c) days of school or work missed; (d) unscheduled medical visits; (e) comfort of parents with management of AOM without antibiotics for future episodes 2 trained research assistants blinded to group assignment conducted standardised, structured telephone interviews with the parents at day 4 to 6, day 11 to 14, day 30 and day 40 after enrolment
Notes	Investigator-blinded study comparing immediate versus delayed antibiotic prescribing (prescription provided and advised to fill only if symptoms worsen or do not improve)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-assisted randomisation
Allocation concealment (selection bias)	Low risk	Sealed opaque envelopes
Other bias	Low risk	ITT analysis - yes, baseline characteristics - balanced
Blinding of participants and personnel (performance bias)	Unclear risk	Investigator-blinded study, parents not blinded
Incomplete outcome data (attrition bias)	Unclear risk	Loss to follow-up at day 4 to 6 treatment: N = 12 (8%) and expectant observation: N = 6 (4%)

Thalin 1985

Methods	**Randomised -** yes, block randomisation, method of random sequence generation not described **Concealment of allocation -** adequate **Double-blind -** yes **Intention-to-treat (ITT) -** unclear **Loss to follow-up -** described **Design -** parallel
Participants	**N -** 293 children (N = 293 children included in analysis) **Age -** between 2 and 15 years **Setting -** secondary care: department of otorhinolaryngology in Halmstad (Sweden) **Inclusion criteria -** purulent acute otitis media (AOM) (no further criteria described) **Exclusion criteria -** antibiotic treatment or AOM episode < 4 weeks prior to randomisation, suspected penicillin allergy, presence of ventilation tubes, sensorineural hearing loss, existence of concomitant infection for which antibiotic treatment was required and chronic diseases **Baseline characteristics -** not described
Interventions	**Tx -** phenoxymethyl penicillin 50 mg/kg/day twice daily for 7 days; N = 159 (N = 159 included in analysis) **C -** matching placebo in 2 doses for 7 days; N = 158 (N = 158 included in analysis) **Use of additional medication -** all children were given nose drops containing oxymetazoline chloride and, if needed, analgesics (paracetamol)
Outcomes	**Primary outcome -** treatment failure (defined as remaining non-negligible symptoms such as pain and fever, insufficient resolution of infectious signs during treatment period of 7 days, or both **Secondary outcomes -** (a) resolution of symptoms over time; (b) AOM relapses; (c) tympanometry, audiometry, or both, results at 4 weeks The children were examined at day 0, days 3 to 4, days 8 to 10 and at 4 weeks Parents were instructed to record symptoms (i.e. temperature, otalgia, discharge from ear and consumption of supplied symptomatic drugs)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Block randomisation, method of random sequence generation not described
Allocation concealment (selection bias)	Low risk	Randomisation list was kept by the clinical pharmacologist of the hospital and not disclosed to the investigators until the clinical trial was completed
Other bias	Unclear risk	ITT analysis - unclear; baseline characteristics - not described

Thalin 1985 (*Continued*)

Blinding of participants and personnel (performance bias)	Low risk	Placebo with same taste and appearance of penicillin
Incomplete outcome data (attrition bias)	Low risk	No children lost to follow-up for primary analysis

Tähtinen 2011

Methods	**Randomised -** yes, computerised random number generator with block length of 10 **Concealment of allocation -** adequate **Double-blind -** yes **Intention-to-treat (ITT) -** yes **Loss to follow-up -** described **Design -** parallel
Participants	**N -** 322 children (N = 319 children were included in analysis) **Age -** between 6 months and 3 years **Setting -** general practice: health care centre of Turku (Finland) **Inclusion criteria -** acute otitis media (AOM) based on 3 criteria: (a) middle-ear fluid had to be detected by means of pneumatic otoscopic examination that showed at least 2 of the following tympanic membrane findings: bulging position, decreased or absent mobility, abnormal colour or opacity not due to scarring, or air fluid interfaces; (b) at least 1 of the following acute inflammatory signs in the tympanic membrane had to be present: distinct erythematous patches or streaks or increased vascularity over full, bulging, or yellow tympanic membrane; (c) presence of acute symptoms such as fever, otalgia or respiratory symptoms **Exclusion criteria -** ongoing antibiotic treatment; AOM with spontaneous perforation of the tympanic membrane; systemic or nasal steroid therapy within 3 preceding days; antihistamine, oseltamivir or a combination therapy within 3 preceding days; contraindication to penicillin or amoxicillin; presence of ventilation tube; severe infection requiring antibiotic treatment; documented Epstein-Barr virus infection within 7 preceding days; Down's syndrome or other condition affecting middle-ear diseases; known immunodeficiency **Baseline characteristics -** balanced
Interventions	**Tx -** amoxicillin-clavulanate 40-5.7 mg/kg daily in 2 doses for 7 days ; N = 162 (N = 161 included in analysis) **C -** matching placebo in 2 doses for 7 days; N = 160 (N = 158 included in analysis) **Use of additional medication -** the use of analgesics and antipyretic agents were encouraged and the use of analgesic ear drops and decongestive nose drops or sprays was allowed
Outcomes	**Primary outcome -** time to treatment failure (i.e. a composite end point consisting of 6 independent components: (a) no improvement in overall condition at day 2, (b) worsening of the child's overall condition at any time, (c) no improvement in otoscopic signs at day 7, (d) perforation of tympanic membrane at any time, (e) severe infection (e.g. mastoiditis or pneumonia) necessitating systemic open-label antimicrobial treatment at any time, (f) any other reason for stopping the study drug at any time

	Secondary outcomes - assessed by study physician - (a) time to the initiation of rescue treatment; (b) time to development of contralateral AOM; - diary symptom assessment; (c) resolution of symptoms; (d) use of analgesics Parents were given a diary to record symptoms, doses of study drugs and any other medications and adverse events First visit after enrolment (= day 0) was scheduled at day 2. End-of-treatment visit was scheduled at day 7
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computerised random number generator with block length of 10
Allocation concealment (selection bias)	Low risk	Concealment of allocation by the pharmacist (independent to trial team) by labelling the identical opaque study drug containers with allocation numbers; allocation list was kept at the paediatric infectious disease ward behind locked doors
Other bias	Low risk	ITT analysis - yes, baseline characteristics - balanced
Blinding of participants and personnel (performance bias)	Low risk	Placebo with same taste and appearance of amoxicillin-clavulanate
Incomplete outcome data (attrition bias)	Low risk	Loss to follow-up - treatment: N = 1 (1%) and placebo: N = 2 (1%)

vanBuchem 1981a

Methods	**Randomised -** yes, method of randomisation not described **Concealment of allocation -** adequate **Double-blind -** yes **Intention-to-treat (ITT) -** unclear **Loss to follow-up -** reasons not described, unclear from which treatment group patients were excluded **Design -** 2 x 2 factorial design
Participants	**N -** 202 children (N = 171 children included in analysis; N = 31 were excluded from the study) **Age -** between 2 and 12 years **Setting -** both general practice and secondary care: 12 general practitioners in or near Tilburg (the Netherlands) recruited patients and referred them to 1 of the 3 otorhino-

	laryngologists, which excluded those cases where there was disagreement with the diagnosis **Inclusion criteria -** acute otitis media (AOM) was based on history and clinical picture (i.e. diffuse redness, bulging of the eardrum, or both) **Exclusion criteria -** antibiotic treatment < 2 weeks prior to randomisation, chronic otitis or otitis media serosa, contraindication for antibiotic treatment **Baseline characteristics -** balanced
Interventions	**Tx -** sham myringotomy and amoxicillin 250 mg 3 times daily for 7 days; N = 47 **C -** sham myringotomy and matching placebo for 7 days; N = 40 **Use of additional medication -** all participants were allowed to use decongestive nose drops and analgesic suppositories (i.e. children aged 2 to 7 years: acetylsalicylic acid 50 mg, phenacetin 50 mg, phenobarbitone 15 mg, codeine phosphate 2.5 mg, caffeine 1. 25 mg; children aged 8 to 12 years: acetylsalicylic acid 100 mg, phenacetin 100 mg, phenobarbitone 30 mg, codeine phosphate 5 mg, caffeine 2.5 mg
Outcomes	**Main outcomes -** (a) parent report of pain at day 0, 1 and 7; (b) otoscopic findings at day 0, 1 and 7; (c) discharge from ear at day 1, 7 and 14; (d) mean temperature at day 0, 1 and 7; (e) AOM relapses at 6 months; (f) audiogram findings after 4 and 8 weeks
Notes	vanBuchem 1981a is the 2 arms without myringotomy

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not described
Allocation concealment (selection bias)	Low risk	Randomisation performed by otorhinolaryngologists; general practitioner and parent/child were outcome assessors and remained blinded
Other bias	Unclear risk	ITT analysis - unclear, baseline characteristics - balanced
Blinding of participants and personnel (performance bias)	Low risk	Sham myringotomy and placebo was similar with amoxicillin with regard to appearance and taste
Incomplete outcome data (attrition bias)	Unclear risk	Loss to follow-up/exclusions - N = 31 (15%). Reasons not described

vanBuchem 1981b

Methods	**Randomised -** yes, method of randomisation not described **Concealment of allocation -** adequate **Double-blind -** yes **Intention-to-treat (ITT) -** unclear **Loss to follow-up -** reasons not described, unclear from which treatment group patients were excluded **Design -** 2 x 2 factorial design
Participants	**N -** 202 children (N = 171 children included in analysis; N = 31 were excluded from the study) **Age -** between 2 and 12 years **Setting -** both general practice and secondary care: 12 general practitioners in or near Tilburg (the Netherlands) recruited patients and referred them to 1 of the 3 otorhinolaryngologists which excluded those cases where there was disagreement with the diagnosis **Inclusion criteria -** acute otitis media (AOM) was based on history and clinical picture (i.e. diffuse redness, bulging of the eardrum, or both) **Exclusion criteria -** antibiotic treatment < 2 weeks prior to randomisation, chronic otitis or otitis media serosa, contraindication for antibiotic treatment **Baseline characteristics -** balanced
Interventions	**Tx -** myringotomy and amoxicillin 250 mg 3 times daily for 7 days; N = 48 **C -** myringotomy and matching placebo for 7 days; N = 36 **Use of additional medication -** all participants were allowed to use decongestive nose drops and analgesic suppositories (i.e. children aged 2 to 7 years: acetylsalicylic acid 50 mg, phenacetin 50 mg, phenobarbitone 15 mg, codeine phosphate 2.5 mg, caffeine 1. 25 mg; children aged 8 to 12 years: acetylsalicylic acid 100 mg, phenacetin 100 mg, phenobarbitone 30 mg, codeine phosphate 5 mg, caffeine 2.5 mg
Outcomes	**Main outcomes -** (a) parent report of pain at day 0, 1 and 7, (b) otoscopic findings at day 0, 1 and 7; (c) discharge from ear at day 1, 7 and 14; (d) mean temperature at day 0, 1 and 7; (e) AOM relapses at 6 months; (f) audiogram findings after 4 and 8 weeks
Notes	vanBuchem 1981b is the 2 arms with myringotomy

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not described
Allocation concealment (selection bias)	Low risk	Randomisation performed by otorhinolaryngologists; general practitioner and parent/child were outcome assessors and remained blinded
Other bias	Unclear risk	ITT analysis - unclear, baseline characteristics - balanced

vanBuchem 1981b (*Continued*)

Blinding of participants and personnel (performance bias)	Low risk	Sham myringotomy and placebo was similar with amoxicillin with regard to appearance and taste
Incomplete outcome data (attrition bias)	Unclear risk	Loss to follow-up/exclusions - N = 31 (15%). Reasons not described

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Arguedas 2011	No comparison of antibiotic to placebo or expectant observation: trial comparing single-dose extended-release azithromycin versus a 10-day regimen of amoxicillin/clavulanate
Casey 2012	No comparison of antibiotic to placebo or expectant observation: trial comparing amoxicillin/clavulanate high dose versus cefdinir
Chaput 1982	Short versus long course of therapy
Engelhard 1989	No comparison of antibiotic to placebo; the 3 arms were Augmentin, myringotomy, or both
Liu 2011	No comparison of antibiotic to placebo or expectant observation: trial comparing single oral doses azithromycin of extended-release versus immediate-release formulations
Ostfeld 1987	Non-randomised study
Rudberg 1954	Non-randomised study: assigned "randomly" based on case-number but then allowed to change groups
Ruohola 2003	Conducted in children with ventilation tubes
Sarrell 2003	No comparison of antibiotic to placebo. Method of randomisation not provided and groups appear to be unbalanced at baseline
Tähtinen 2012	Secondary analysis of placebo-controlled trial. This study included the total group of children allocated to immediate antimicrobial treatment (N = 161) and a subgroup of children from the placebo group that received delayed antibiotics (N = 53). As a consequence, comparability of prognosis achieved through randomisation is violated, producing groups of children that are incomparable which may lead to biased effect estimates
vanBuchem 1985	Non-randomised study

DATA AND ANALYSES

Comparison 1. Antibiotics versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain	11		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Pain at 24 hours	6	1394	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.78, 1.01]
1.2 Pain at 2 to 3 days	7	2320	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.57, 0.86]
1.3 Pain at 4 to 7 days	7	1263	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.66, 0.95]
2 Abnormal tympanometry	7		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 4 to 6 weeks	7	2114	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.83, 1.01]
2.2 3 months	3	809	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.76, 1.24]
3 Tympanic membrane perforation	4	991	Risk Ratio (M-H, Fixed, 95% CI)	0.37 [0.18, 0.76]
4 Contralateral otitis (in unilateral cases)	4	906	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.25, 0.95]
5 Late AOM recurrences	6	2200	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.78, 1.10]
6 Vomiting, diarrhoea or rash	7	2023	Risk Ratio (M-H, Fixed, 95% CI)	1.34 [1.16, 1.55]

Comparison 2. Immediate antibiotics versus expectant observation

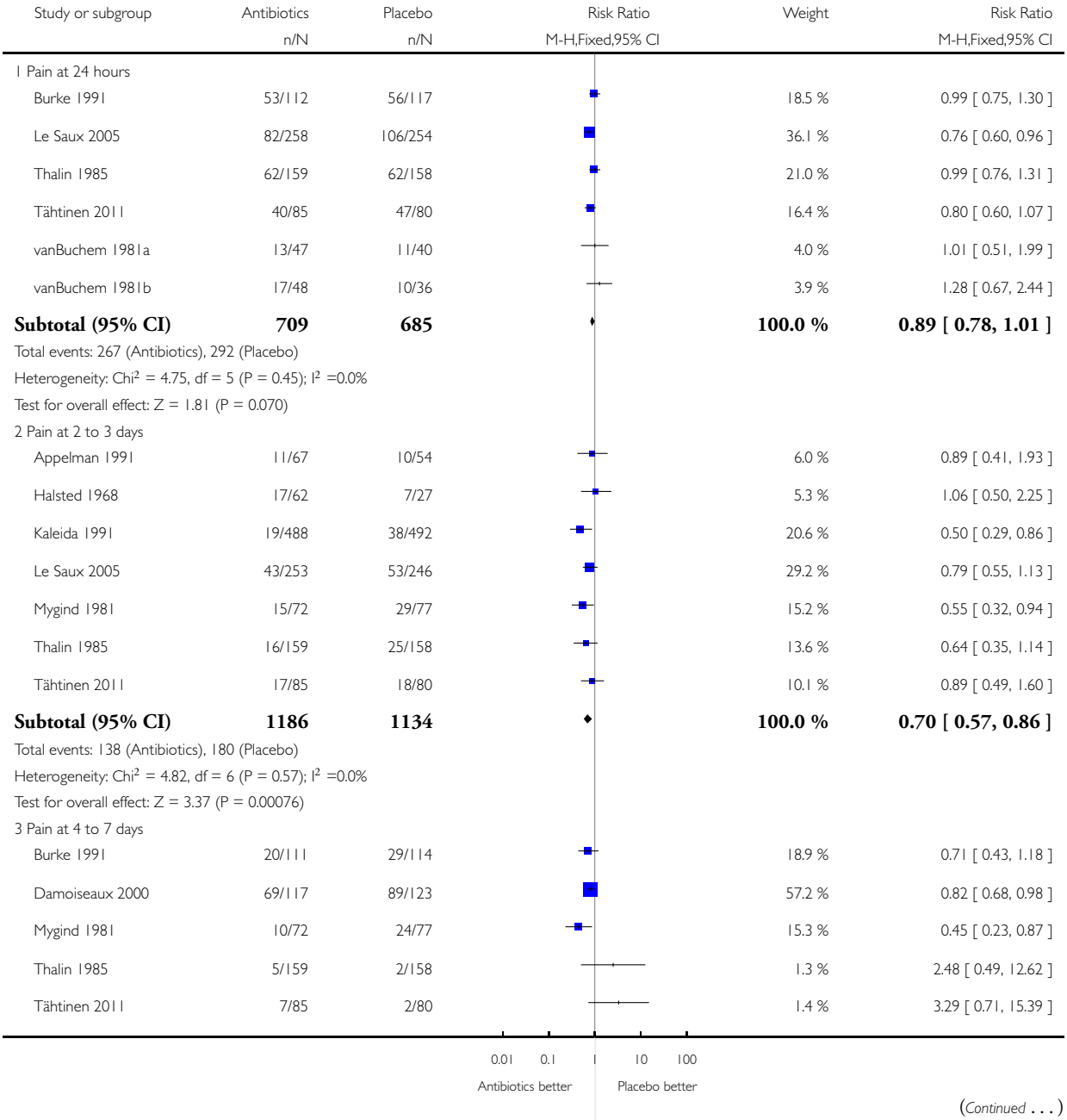
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain at 3 to 7 days	4	959	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.50, 1.12]
2 Tympanic membrane perforation	1	179	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 AOM recurrences	1	209	Risk Ratio (M-H, Fixed, 95% CI)	1.41 [0.74, 2.69]
4 Vomiting, diarrhoea or rash	2	550	Risk Ratio (M-H, Fixed, 95% CI)	1.71 [1.24, 2.36]

Analysis 1.1. Comparison 1 Antibiotics versus placebo, Outcome 1 Pain.

Review: Antibiotics for acute otitis media in children

Comparison: 1 Antibiotics versus placebo

Outcome: 1 Pain

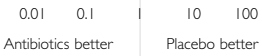


Study or subgroup	Antibiotics n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Pain at 24 hours					
Burke 1991	53/112	56/117		18.5 %	0.99 [0.75, 1.30]
Le Saux 2005	82/258	106/254		36.1 %	0.76 [0.60, 0.96]
Thalin 1985	62/159	62/158		21.0 %	0.99 [0.76, 1.31]
Tähtinen 2011	40/85	47/80		16.4 %	0.80 [0.60, 1.07]
vanBuchem 1981a	13/47	11/40		4.0 %	1.01 [0.51, 1.99]
vanBuchem 1981b	17/48	10/36		3.9 %	1.28 [0.67, 2.44]
Subtotal (95% CI)	**709**	**685**		**100.0 %**	**0.89 [0.78, 1.01]**
Total events: 267 (Antibiotics), 292 (Placebo)					
Heterogeneity: Chi^2 = 4.75, df = 5 (P = 0.45); I^2 =0.0%					
Test for overall effect: Z = 1.81 (P = 0.070)					
2 Pain at 2 to 3 days					
Appelman 1991	11/67	10/54		6.0 %	0.89 [0.41, 1.93]
Halsted 1968	17/62	7/27		5.3 %	1.06 [0.50, 2.25]
Kaleida 1991	19/488	38/492		20.6 %	0.50 [0.29, 0.86]
Le Saux 2005	43/253	53/246		29.2 %	0.79 [0.55, 1.13]
Mygind 1981	15/72	29/77		15.2 %	0.55 [0.32, 0.94]
Thalin 1985	16/159	25/158		13.6 %	0.64 [0.35, 1.14]
Tähtinen 2011	17/85	18/80		10.1 %	0.89 [0.49, 1.60]
Subtotal (95% CI)	**1186**	**1134**		**100.0 %**	**0.70 [0.57, 0.86]**
Total events: 138 (Antibiotics), 180 (Placebo)					
Heterogeneity: Chi^2 = 4.82, df = 6 (P = 0.57); I^2 =0.0%					
Test for overall effect: Z = 3.37 (P = 0.00076)					
3 Pain at 4 to 7 days					
Burke 1991	20/111	29/114		18.9 %	0.71 [0.43, 1.18]
Damoiseaux 2000	69/117	89/123		57.2 %	0.82 [0.68, 0.98]
Mygind 1981	10/72	24/77		15.3 %	0.45 [0.23, 0.87]
Thalin 1985	5/159	2/158		1.3 %	2.48 [0.49, 12.62]
Tähtinen 2011	7/85	2/80		1.4 %	3.29 [0.71, 15.39]

(*Continued* . . .)

(. . . *Continued*)

Study or subgroup	Antibiotics n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
vanBuchem 1981a	3/46	4/38		2.9 %	0.62 [0.15, 2.60]
vanBuchem 1981b	5/48	4/35		3.1 %	0.91 [0.26, 3.15]
Subtotal (95% CI)	**638**	**625**		**100.0 %**	**0.79 [0.66, 0.95]**
Total events: 119 (Antibiotics), 154 (Placebo)					
Heterogeneity: Chi^2 = 8.51, df = 6 (P = 0.20); I^2 =29%					
Test for overall effect: Z = 2.56 (P = 0.010)					



Analysis 1.2. Comparison 1 Antibiotics versus placebo, Outcome 2 Abnormal tympanometry.

Review: Antibiotics for acute otitis media in children

Comparison: 1 Antibiotics versus placebo

Outcome: 2 Abnormal tympanometry

Study or subgroup	Antibiotics n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 4 to 6 weeks					
Appelman 1991	21/51	25/45		5.6 %	0.74 [0.49, 1.13]
Burke 1991	41/112	41/116		8.5 %	1.04 [0.73, 1.46]
Damoiseaux 2000	69/107	70/105		14.9 %	0.97 [0.80, 1.18]
Kaleida 1991	151/329	169/328		35.6 %	0.89 [0.76, 1.04]
Le Saux 2005	68/233	77/222		16.6 %	0.84 [0.64, 1.10]
Mygind 1981	23/72	25/77		5.1 %	0.98 [0.62, 1.57]
Thalin 1985	65/159	65/158		13.7 %	0.99 [0.76, 1.29]
Subtotal (95% CI)	**1063**	**1051**		**100.0 %**	**0.92 [0.83, 1.01]**
Total events: 438 (Antibiotics), 472 (Placebo)					
Heterogeneity: Chi^2 = 2.72, df = 6 (P = 0.84); I^2 =0.0%					
Test for overall effect: Z = 1.77 (P = 0.076)					
2 3 months					

(*Continued* . . .)

(. . . *Continued*)

Study or subgroup	Antibiotics n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Burke 1991	20/111	31/111		31.9 %	0.65 [0.39, 1.06]
Le Saux 2005	58/228	47/210		50.3 %	1.14 [0.81, 1.59]
Mygind 1981	18/72	18/77		17.9 %	1.07 [0.61, 1.89]
Subtotal (95% CI)	**411**	**398**		**100.0 %**	**0.97 [0.76, 1.24]**
Total events: 96 (Antibiotics), 96 (Placebo)					
Heterogeneity: Chi^2 = 3.56, df = 2 (P = 0.17); I^2 =44%					
Test for overall effect: Z = 0.26 (P = 0.80)					

Analysis 1.3. Comparison 1 Antibiotics versus placebo, Outcome 3 Tympanic membrane perforation.

Review: Antibiotics for acute otitis media in children

Comparison: 1 Antibiotics versus placebo

Outcome: 3 Tympanic membrane perforation

Study or subgroup	Antibiotics n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Burke 1991	0/114	2/118		9.4 %	0.21 [0.01, 4.26]
Hoberman 2011	1/144	7/147		26.6 %	0.15 [0.02, 1.17]
Mygind 1981	7/72	12/77		44.6 %	0.62 [0.26, 1.50]
Tähtinen 2011	1/161	5/158		19.4 %	0.20 [0.02, 1.66]
Total (95% CI)	**491**	**500**		**100.0 %**	**0.37 [0.18, 0.76]**
Total events: 9 (Antibiotics), 26 (Placebo)					
Heterogeneity: Chi^2 = 2.59, df = 3 (P = 0.46); I^2 =0.0%					
Test for overall effect: Z = 2.70 (P = 0.0069)					
Test for subgroup differences: Not applicable					

Analysis 1.4. Comparison 1 Antibiotics versus placebo, Outcome 4 Contralateral otitis (in unilateral cases).

Review: Antibiotics for acute otitis media in children

Comparison: 1 Antibiotics versus placebo

Outcome: 4 Contralateral otitis (in unilateral cases)

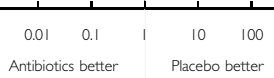
Study or subgroup	Antibiotics n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Burke 1991	29/98	33/102		36.1 %	0.91 [0.60, 1.38]
Hoberman 2011	13/161	29/158		30.9 %	0.44 [0.24, 0.81]
Mygind 1981	2/64	6/63		12.7 %	0.33 [0.07, 1.56]
Thalin 1985	4/130	17/130		20.3 %	0.24 [0.08, 0.68]
Total (95% CI)	**453**	**453**		**100.0 %**	**0.49 [0.25, 0.95]**

Total events: 48 (Antibiotics), 85 (Placebo)

Heterogeneity: $Tau^2 = 0.28$; $Chi^2 = 8.79$, df = 3 (P = 0.03); $I^2 = 66\%$

Test for overall effect: Z = 2.12 (P = 0.034)

Test for subgroup differences: Not applicable



Analysis 1.5. Comparison 1 Antibiotics versus placebo, Outcome 5 Late AOM recurrences.

Review: Antibiotics for acute otitis media in children

Comparison: 1 Antibiotics versus placebo

Outcome: 5 Late AOM recurrences

Study or subgroup	Antibiotics n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Hoberman 2011	19/119	13/70		7.5 %	0.86 [0.45, 1.63]
Kaleida 1991	125/448	123/446		56.6 %	1.01 [0.82, 1.25]
Le Saux 2005	27/248	39/236		18.3 %	0.66 [0.42, 1.04]
Mygind 1981	19/72	21/77		9.3 %	0.97 [0.57, 1.65]
Thalin 1985	9/159	7/158		3.2 %	1.28 [0.49, 3.35]
vanBuchem 1981a	9/92	10/75		5.1 %	0.73 [0.31, 1.71]
Total (95% CI)	**1138**	**1062**		**100.0 %**	**0.93 [0.78, 1.10]**

Total events: 208 (Antibiotics), 213 (Placebo)

Heterogeneity: Chi^2 = 3.60, df = 5 (P = 0.61); I^2 =0.0%

Test for overall effect: Z = 0.90 (P = 0.37)

Test for subgroup differences: Not applicable

Analysis 1.6. Comparison 1 Antibiotics versus placebo, Outcome 6 Vomiting, diarrhoea or rash.

Review: Antibiotics for acute otitis media in children

Comparison: 1 Antibiotics versus placebo

Outcome: 6 Vomiting, diarrhoea or rash

Study or subgroup	Antibiotics n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Burke 1991	53/114	36/118		17.3 %	1.52 [1.09, 2.13]
Damoiseaux 2000	20/117	12/123		5.7 %	1.75 [0.90, 3.42]
Hoberman 2011	49/144	36/147		17.4 %	1.39 [0.97, 2.00]
Le Saux 2005	43/235	47/240		22.7 %	0.93 [0.64, 1.36]
Mygind 1981	3/72	1/77		0.5 %	3.21 [0.34, 30.14]
Thalin 1985	1/159	1/158		0.5 %	0.99 [0.06, 15.75]
Tähtinen 2011	105/161	73/158		36.0 %	1.41 [1.15, 1.73]
Total (95% CI)	**1002**	**1021**		**100.0 %**	**1.34 [1.16, 1.55]**

Total events: 274 (Antibiotics), 206 (Placebo)

Heterogeneity: $Chi^2 = 5.68$, df = 6 (P = 0.46); $I^2 = 0.0\%$

Test for overall effect: Z = 4.02 (P = 0.000057)

Test for subgroup differences: Not applicable

Analysis 2.1. Comparison 2 Immediate antibiotics versus expectant observation, Outcome 1 Pain at 3 to 7 days.

Review: Antibiotics for acute otitis media in children

Comparison: 2 Immediate antibiotics versus expectant observation

Outcome: 1 Pain at 3 to 7 days

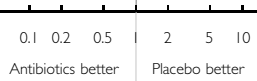
Study or subgroup	Antibiotics n/N	Expectant observation n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Little 2001	26/151	44/164		28.2 %	0.64 [0.42, 0.99]
McCormick 2005	24/102	38/98		28.3 %	0.61 [0.40, 0.93]
Neumark 2007	2/92	4/87		5.2 %	0.47 [0.09, 2.52]
Spiro 2006	89/133	85/132		38.4 %	1.04 [0.87, 1.24]
Total (95% CI)	**478**	**481**		**100.0 %**	**0.75 [0.50, 1.12]**

Total events: 141 (Antibiotics), 171 (Expectant observation)

Heterogeneity: $Tau^2 = 0.10$; $Chi^2 = 10.28$, df = 3 (P = 0.02); $I^2 = 71\%$

Test for overall effect: Z = 1.40 (P = 0.16)

Test for subgroup differences: Not applicable



Analysis 2.2. Comparison 2 Immediate antibiotics versus expectant observation, Outcome 2 Tympanic membrane perforation.

Review: Antibiotics for acute otitis media in children

Comparison: 2 Immediate antibiotics versus expectant observation

Outcome: 2 Tympanic membrane perforation

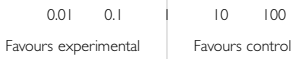
Study or subgroup	Antibiotics n/N	Expectant observation n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Neumark 2007	0/92	0/87		0.0 [0.0, 0.0]
Total (95% CI)	**92**	**87**		**0.0 [0.0, 0.0]**

Total events: 0 (Antibiotics), 0 (Expectant observation)

Heterogeneity: not applicable

Test for overall effect: Z = 0.0 (P < 0.00001)

Test for subgroup differences: Not applicable



Analysis 2.3. Comparison 2 Immediate antibiotics versus expectant observation, Outcome 3 AOM recurrences.

Review: Antibiotics for acute otitis media in children

Comparison: 2 Immediate antibiotics versus expectant observation

Outcome: 3 AOM recurrences

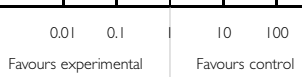
Study or subgroup	Antibiotics n/N	Expectant observation n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
McCormick 2005	20/109	13/100		100.0 %	1.41 [0.74, 2.69]
Total (95% CI)	**109**	**100**		**100.0 %**	**1.41 [0.74, 2.69]**

Total events: 20 (Antibiotics), 13 (Expectant observation)

Heterogeneity: not applicable

Test for overall effect: Z = 1.05 (P = 0.29)

Test for subgroup differences: Not applicable



Analysis 2.4. Comparison 2 Immediate antibiotics versus expectant observation, Outcome 4 Vomiting, diarrhoea or rash.

Review: Antibiotics for acute otitis media in children

Comparison: 2 Immediate antibiotics versus expectant observation

Outcome: 4 Vomiting, diarrhoea or rash

Study or subgroup	Antibiotics n/N	Expectant observation n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Little 2001	31/135	22/150		45.4 %	1.57 [0.95, 2.57]
Spiro 2006	46/133	25/132		54.6 %	1.83 [1.20, 2.79]
Total (95% CI)	**268**	**282**		**100.0 %**	**1.71 [1.24, 2.36]**
Total events: 77 (Antibiotics), 47 (Expectant observation)					
Heterogeneity: Chi^2 = 0.21, df = 1 (P = 0.64); I^2 =0.0%					
Test for overall effect: Z = 3.26 (P = 0.0011)					
Test for subgroup differences: Not applicable					

APPENDICES

Appendix 1. Previous search

Several electronic databases were used to compile relevant published RCTs of antibiotic treatment of AOM in children. The Cochrane Controlled Trials Register, MEDLINE and Current Contents were searched from 1966 to January 2000 by an expert librarian in conjunction with one researcher, using combinations of "OTITIS MEDIA" and a search strategy described by (Dickersin 1994) for optimally identifying controlled trials. In addition, titles in Index Medicus were checked from 1958 to 1965. The references of all relevant retrieved trials were checked to identify other articles.

The search was updated in March 2003, and again in July 2008. We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*, 2008, issue 2) which contains the ARI Group's Specialized Register; MEDLINE (1966 to June week 4 2008); OLDMEDLINE (1958 to 1965); EMBASE (January 1990 to July 2008); and Current Contents (1966 to July 2008). The bibliographies of relevant articles were checked. A forward search of relevant articles was conducted in Web of Science®.

The following search strategy was run on MEDLINE (Ovid) combined with terms from Phase 1 and 2 of the Cochrane highly sensitive search strategy for identifying reports of RCTs (Lefebvre 2011). Modified terms were used to search the other databases:

MEDLINE (Ovid)

#1 exp Otitis Media/
#2 exp Otitis Media with Effusion/
#3 exp Otitis Media, Suppurative/
#4 glue ear.mp.
#5 otitis media.mp.
#6 OME.mp.
#7 AOM.mp.
#8 #1 or #2 or #3 or #4 or #5 or #6 or #7
#9 exp Anti-Bacterial Agents/
#10 exp Drug Therapy/
#11 exp Anti-Infective Agents/
#12 antibiotic$.mp.
#13 #9 or #10 or #11 or #12
#14 #8 and #13
There were no language or publication restrictions.

Appendix 2. Embase.com search strategy

18 #14 AND #17
17 #15 OR #16
16 random*:ab,ti OR placebo*:ab,ti OR factorial*:ab,ti OR crossover*:ab,ti OR 'cross-over':ab,ti OR 'cross over':ab,ti OR volunteer*:ab,ti OR assign*:ab,ti OR allocat*:ab,ti
15 'randomized controlled trial'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp
14 #4 AND #13
13 #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12
12 ampicillin*:ab,ti OR cephalosporin*:ab,ti OR macrolide*:ab,ti OR penicillin*:ab,ti OR amoxycillin*:ab,ti OR amoxicillin*:ab,ti OR cefdinir*:ab,ti OR cefpodoxime*:ab,ti OR cefuroxime*:ab,ti OR
azithromycin*:ab,ti OR clarithromycin*:ab,ti OR erythromycin*:ab,ti
11 'penicillin g'/exp
10 'macrolide'/exp
9 'cephalosporin derivative'/exp
8 'ampicillin'/exp
7 antibiotic*:ab,ti OR antibacterial*:ab,ti
6 'drug therapy'/de OR 'antiinfective agent'/de
5 'antibiotic agent'/exp
4 #1 OR #2 OR #3
3 ('middle ear' NEAR/5 (inflam* OR infect*)):ab,ti
2 'otitis media':ab,ti OR 'glue ear':ab,ti OR 'glue ears':ab,ti OR ome:ab,ti OR aom:ab,ti
1 'otitis media'/exp

Appendix 3. Current Contents search strategy

# 3	578	#2 AND #1 *Databases=CM, LS Timespan=All Years* *Lemmatization=On*

(*Continued*)

# 2	528,401	Topic=(random* or placebo* or crossover* or "cross over" or allocat* or ((doubl* or singl*) NEAR/1 blind*)) OR Title=(trial) *Databases=CM, LS Timespan=All Years* *Lemmatization=On*
# 1	2,624	Topic=(otitis or "glue ear" or ("middle ear" NEAR/3 (infect* or inflam*)) or ome or aom) AND Topic=(antibiotic* or antibacterial* or antiinfective* or ampicillin* or cephalosporin* or macrolide* or amoxicillin* or amoxycillin* or penicillin* or cefdinir* or cefpodoxime* or cefuroxime* or azithromycin* or clarithromycin* or erythromycin*) *Databases=CM, LS Timespan=All Years* *Lemmatization=On*

Appendix 4. CINAHL search strategy

S30 S19 and S29
S29 S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28
S28 (MH "Quantitative Studies")
S27 TI placebo* or AB placebo*
S26 (MH "Placebos")
S25 TI random* or AB random*
S24 (MH "Random Assignment")
S23 TI (singl* blind* or doubl* blind* or tripl* blind* or trebl* blind* or singl* mask* or doubl* mask* or tripl* mask* or trebl* mask*) or AB (singl* blind* or doubl* blind* or tripl* blind* or trebl* blind* or singl* mask* or doubl* mask* or tripl* mask* or trebl* mask*)
S22 TI clinic* N1 trial* or AB clinic* N1 trial*
S21 PT clinical trial
S20 (MH "Clinical Trials+")
S19 S7 and S18
S18 S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17
S17 TI (ampicillin* or cephalosporin* or macrolide* or amoxicillin* or amoxycillin* or penicillin* or cefdinir* or cefpodoxime* or cefuroxime* or azithromycin* or clarithromycin* or erythromycin*) or AB (ampicillin* or cephalosporin* or macrolide* or amoxicillin* or amoxycillin* or penicillin* or cefdinir* or cefpodoxime* or cefuroxime* or azithromycin* or clarithromycin* or erythromycin*)
S16 (MH "Penicillins+")
S15 (MH "Antibiotics, Macrolide+")
S14 (MH "Cephalosporins+")
S13 (MH "Ampicillin+")
S12 TI antibacterial* or AB antibacterial*
S11 TI antibiotic* or AB antibiotic*
S10 (MH "Antiinfective Agents")
S9 (MH "Drug Therapy")
S8 (MH "Antibiotics+")
S7 S1 or S2 or S3 or S4 or S5 or S6
S6 TI (aom or ome) or AB (aom or ome)
S5 TI middle ear inflam* or AB middle ear inflam*
S4 TI middle ear infect* or AB middle ear infect*
S3 AB glue ear* or TI glue ear*
S2 TI otitis media or AB otitis media
S1 (MH "Otitis Media+")

Appendix 5. LILACS search strategy

> Search > (MH:"otitis media" OR "otitis media" OR "Otite Média" OR MH:C09.218.705.633$) AND (MH:"Anti-Bacterial Agents" OR antibiotic$ OR Antibacterianos OR Antibióticos OR MH:"Drug Therapy" OR Quimioterapia OR "Terapia por Drogas" OR Farmacoterapia OR MH:"Anti-Infective Agents" OR Antiinfecciosos OR MH:ampicillin OR Ampicilina OR ampicillin$ OR MH:D02.065.589.099.750.750.050$ OR MH:D02.886.108.750.750.050$ OR MH:D03.438.460.825.750.050$ OR MH:D03.605.084.737.750.050$ OR D04.075.080.875.099.221.750.750.050$ OR MH:cephalosporins OR cephalosporin$ OR Cefalosporinas OR MH:D02.065.589.099.249$ OR D02.886.665.074$ OR D04.075.080.875.099.221.249$ OR MH:macrolides OR macrolide$ OR Macrólidos OR Macrolídeos OR D02.540.505$ OR D02.540.576.500$ OR D04.345.674.500$ OR MH:penicillins OR penicillin$ OR Penicilinas OR MH:D02.065.589.099.750$ OR D02.886.108.750$ OR D03.438.260.825$ OR D03.605.084.737$ OR D04.075.080.875.099.221.750$ OR amoxicillin$ OR Amoxicilina OR cefdinir OR cefpodoxim$ OR cefuroxim$ OR azithromycin$ OR Azitromicina OR clarithromycin$ OR Claritromicina OR erythromycin OR Eritromicina) > clinical˙trials

F E E D B A C K

Antibiotics for AOM, 22 November 2000

Summary

1. Types of interventions includes surgical procedures versus placebo which are not dealt with in this review and should therefore be deleted.
2. The authors included only six studies in the analysis but in 1994 another meta-analysis by Rosenfeld and colleagues to which the authors refer was published which included 33 randomized trials with 5400 children. Were any studies with a no-treatment control excluded and if so why?
3. The meta-analysis by Rosenfeld is only mentioned in the text; there is no reference to it. How many patients were included in the meta-analysis?
4. It is stated that trials analysed on an intention to treat basis were preferred. This indicates that other trials were excluded which does not seem reasonable?
5. The description of the factorial trial is unclear; I suppose the authors excluded all patients who were randomised to myringotomy?
6. In the trial by Laxdal the control group was more closely monitored. The trial therefore violates the principle that all other Traitement etc. should be the same in the two randomised groups and it should therefore be excluded.
7. The strategy described by Dickersin lacks a publication year and it is not cited in the references.
8. The search was done in August 1994 and the Cochrane review was published in April 1997. The search should therefore have been updated before publication since Cochrane reviews are meant to be up-to-date.
9. There is no information whether the original authors and the pharmaceutical industry were contacted about additional data including unpublished trials and trials not registered in Medline. Useful trial data might be expected to be available in books published in connection with symposia arranged by the drug industry for example.
10. What is quality methodology?
11. The term blinded randomisation should be avoided since it may be confused with blinded treatments; the term concealed allocation should be used.
12. The elaborated quality assessment scale for the trials does not appear under Results and should therefore be deleted.
13. The authors refer to Rosenfeld's meta-analysis when they state that 80% of the children have recovered spontaneously after 24 hours. Since such a percentage refers to untreated patients it raises the question why the authors did not use their own data? If these data are used in a meta-analysis of the risk difference the NNTB will be 23 not 12 as stated in the Cochrane review.
14. For several of the excluded studies the authors gave no reason for the exclusion.
15. There should be a cross-reference to the authors' nearly identical review in the BMJ (24 May 1997).

Reply

The changes made were:

1. We updated the search. (see Johansen criticism 7 & 8). No recent trials were found but we recognised that the Appelman trial qualifies (originally we had thought this was only prevention of recurrent otitis, rather than treatment of acute otitis in children with a recurrent episode).
2. We have corrected and updated the Relative Risk Reduction and consequent Number-Needed-to-Treat (see Johansen criticism 13).
3. We have separate the four arms of the Van Buchem factorial trial, and treated this as "two" trials (i.e., two separate strata): (a) without myringotomy - antibiotics versus placebo (b) with myringotomy - antibiotics versus placebo. (see Johansen criticism 5)
4. As suggested by Andrew Herxheimer, we have added several references including (a) Chris Cates BMJ, and (b) Kozrskyj's meta-analysis of short versus long duration of antibiotics (rather than just the de Saintonge paper).
5. We have made small text changes in response to Johansen's criticisms 5 (description added), 7 (dropped), 10 (- methodological quality), 11 (- allocation concealment), 13 (corrected in text), 14 (exclusions explained), and 15 (reference added).
6. As we have pointed out to Johansen in the BMJ correspondence, and point out in the discussion here, the Rosenfeld meta-analysis is largely concerned with comparison between antibiotics. (see Johansen criticism 2 & 3).

Contributors

Helle Krogh Johansen
Peter C. Gøtzsche

Antibiotic versus placebo for acute otitis media, 22 November 2010

Summary

This excellent and important review was completed in 1996, and I hope it will soon be updated. It is especially worth noting and discussing the new study by Christopher Cates (BMJ 13 March 1999, p715-6), who has successfully tried a method in his general practice of substantially reducing the use of antibiotic in children with acute otitis media. This would considerably strengthen the 'implications for practice' in the conclusion.
I would like to suggest that in updating this review the objectives be amended and the trial by Chaput de Saintonge et al be added, because it contributes an important piece of evidence about the duration of amoxicillin therapy. The review concludes that some children will benefit from antibiotic treatment, and it would be valuable to say (as a result of the Chaput trial) that the evidence indicates that a 3-day course is no less effective than a 10-day course.

Reply

Chris and I have revised the acute otitis media review. We have made a number of modest changes, though none of these change the conclusions. However, because a new trial is included we've called it a "substantive update".

Contributors

Andrew Herxheimer

Antibiotic versus placebo for acute otitis media, 22 November 2000

Summary

1. I am glad to see this has been updated but the text does not explain what was updated, forcing the reader who wants to know to compare the previous version with the new one. Is it the sentence referring to Cates 99 [in implics for practice] or other points as well?
2. There are embarrassingly many typos in the refs to excluded and additional studies: Chaput de SaintoNGE, amoxyciillin, author not in bold in the first few additional refs, below that several authors' names begin in lower case when they should all begin with a capital.
3. It is implied that no comcrit was received before the final submission date for CL99 issue 3. Is this true? I think I sent one early this year.
CONFLICT OF INTEREST: None.

Reply

Excluded and additional references have been corrected and completed.

Contributors

Andrew Herxheimer

Antibiotic versus placebo for acute otitis media, 22 June 2000

Summary

1. The new study also reported diarrhoea and rashes. Shouldn't it be included in this outcome (side effects) also?
2. I think the methods used for calculating the NNTB should be made explicit.
3. The new trial is important because it looks at a sub-group who were believed to be a greater risk of poor outcomes. In EBM OM Rosenfeld and Bluestone review the study inclusion criteria and state that the meta-analysis 'most likely can be applied to children 2 years of age or older with non severe AOM, and most likely cannot be applied to infants with severe symptoms'. This study provides the best evidence that the conclusions of the meta-analysis do appear to apply to this group. Perhaps this point needs to be emphasised (the peak incidence of AOM is 9 months).
4. I think the comment that 80% resolve spontaneously within 2 to 7 days is now slightly misleading as about 70% of the control children were clinical failures in this new study.
5. The entry in the table 'characteristics of included studies' should be consistent with previous entries.
6. Some typographical errors and inconsistent spelling.

Reply

Thank you for your comments and suggestions.
The Absolute risk difference was used to calculate the NNTB in this systematic review. This has now been stated in the Results section of the review. A comment regarding the application of the conclusions to infants with severe symptoms has been added to the discussion section. The 70% incidence of clinical failure in the Damoiseaux, 2000 study have been included and typographical errors and inconsistencies have been corrected.

Contributors

Peter Morris

Antibiotics for acute otitis media, 19 February 2002

Summary

The second graph (comparison of outcome Abnormal Tympanometry) has wrong labels on the X-axis.
It says 'antibiotics better' (left) and 'placebo worse' (right). The second should probably be 'placebo better'.
The other graphs are correctly labelled.
I certify that I have no affiliations with or involvement in any organisation or entity with a direct financial interest in the subject matter of my
criticisms.

Reply

The label on the x-axis has been corrected and now reads 'Placebo better'.

Contributors

Johannes C van der Wouden

Antibiotics reduce the risk of mastoiditis?, 26 August 2002

Summary

I agree with other commentators that this is a very good and important review. However, I would like some more clarity concerning one statement in your conclusions: Antibiotic treatment may play an important role in reducing the risk of mastoiditis in populations where it is more common.
What is the basis for this statement? In the included studies with more than 2000 children only one mastoiditis case occurred in a patient in a penicillin treated group. In the review you mention two articles concerning the mastoiditis. Firstly, the study of Rudberg (1954), which was excluded since it was not properly randomised. Even if it were, the rate of 17 % of mastoiditis cases is in these times highly unlikely, as is shown in the included studies. The second article by Berman (1995) is a literature review, where only the available literature concerning developing countries were reviewed. The goal of this review was to determine the extent to which otitis media impacts mortality and morbidity in developing countries, not to study the effect of antibiotics on (acute) otitis media or mastoiditis.
In neither of these studies evidence is shown that antibiotic treatment reduces the risk of mastoiditis, certainly not in developed countries. Since I think the rest of the review is excellent, I wonder if you could explain to me the reasons for including this statement in the conclusions.
I certify that I have no affiliations with or involvement in any organisation or entity with a direct financial interest in the subject matter of my criticisms.

Reply

Dear Markus,
We included the caveat about mastoiditis because we, and the reviewers, were concerned about misinterpretation of the results in situations with high rates of mastoiditis. We were mindful that "an absence of evidence is not equal to evidence of absence". Since the trials we analysed did not include high rates of mastoiditis, we can use them as the sole basis. Given that we have two weaker pieces of evidence:
1. The trials do show a modest reduction in other infective complications
2. The excluded Rudberg trial did show dramatic effects that we don't think explicable from the potential biases of that study.
Prudence would then suggest that antibiotics are advisable if there is a substantial risk of mastoiditis,
Regards,
Paul Glasziou
I certify that I have no affiliations with or involvement in any organisation or entity with a direct financial interest in the subject matter of my criticisms.

Contributors

Markus Oei (ENT surgeon)

Incorrect NNTB, 19 June 2005

Summary

I am a bit troubled by the way the conclusions of this review are written. By combining results of treatment at Days 2 to 7 in arriving at a NNTB of 15 one is going to underestimate treatment benefit after 2 days. In your abstract though you say the ARR is 7% and NNTB 15 for some pain after two days. This is simply not correct. If one carefully looks at trials that record pain at the end of day 2 the ARR is in fact 20% giving a NNTB of 5. Clearly acute otitis media is an acute condition and the main benefit of antibiotics is pain control and symptom relief. If this is measured at the end of 2 days the benefits are greater than one would surmise just from reading the review. It would be absurd to do a review of pain relief for biliary colic treated with pethidine and measuring the outcome 7 days later. For acute conditions symptom control in the first few days should be the outcome of interest. NNTB are meaningless unless giving a time period at which they apply. I think the review needs correcting. This is not just of academic interest but of direct relevance to parents and doctors faced with a child with AOM in pain. Unfortunately your review gets quoted uncritically and invariably the NNTB of 15 is given for symptom control after 2 days. I am currently trying to correct a brochure produced here in New Zealand for GPs to give to parents of children with AOM and it uncritically repeats this misleading information. If you want to comment on symptom control after Day 2 DO NOT pool it with data from Day 7 or later!

I certify that I have no affiliations with or involvement in any organisation or entity with a direct financial interest in the subject matter of my criticisms.

Reply

Thankyou for your comment. We agree that we should be clearer about the time frame to which the ARR 7% and NNTB 15 applies. With the availability of results of the individual patient data meta-analysis (Rovers 2006) we are able to obtain a clearer indication of the recovery pattern over time. We have reported this in the text and included an extra figure.

Contributors

Paul Corwin

Comment on two of the meta-analyses, 9 June 2007

Summary

Summary

Feedback: This is a comment on two of the meta-analyses in the Cochrane Review, Glasziou et al. (2004). These analyses are for the outcomes “Vomiting, Diarrhea or Rash” and “Contralateral AOM.”

1) Vomiting, Diarrhea or Rash

First we consider the meta-analysis relating possible adverse effects of treatment. In Glasziou et al. (2004), this is done using the composite outcome “Vomiting, Diarrhea or Rash.” The data used for this meta-analysis are reproduced in the table below.

Outcome: Vomiting, Diarrhea or Rash

Study Treatment Control

Thalin et al. (1985) 1/159 1/158

Burke et al. (1991) 53/114 36/116

Mygind et al. (1981) 3/72 1/77

Damoiseaux et al. (2000) 20 12

We noted five major problems with this meta-analysis. The first relates to clinical heterogeneity. This was manifested in variations in terms of the types of adverse effects recorded, who recorded them (parent or physician) and the time period over which they were

recorded (from 3-4 days to 21 days). In Thalin et al. (1985), the effects were recorded by an ENT physician on days 3-4 or days 8-10. In Burke et al. (1991), they were recorded by a parent in a 21-day diary. In Mygind et al. (1981), it was done with 7 day parental score card. And in Damoiseaux et al. (2000), this was done by a physician on day 4 and day 11.

Another related problem is the use of the outcome "Vomiting, Diarrhea or Rash" as an entity. Vomiting is only reported in Burke et al. (1991). It is not clear whether it was not observed, or observed but not reported in the other studies. Also, in Burkeat al. (1991), as noted, such effects were recorded over a 21-day period while the maximum recording period for the other studies was 11 days. The totals then gave a much higher weight to Burke et al. (1991) than may be appropriate.

A third problem is possible double or triple counting with the use of the composite outcome. For Burke et al. (1991), the group numerator is the sum of the cases for each effect. A number of children may well have had two or three of these effects at the same time.

A fourth problem is also with the numbers used. Damoiseaux et al. (2000) gives two sets of numbers for "de novo diarrhoea," for day 4 and for day 11. Glasziou et al. (2004) uses the day 4 numbers only. The reason for this choice is not clear. It may be better to use the sums of the numbers for the two days (provided this does not involve double counting.)

Further, the group denominators used for Burke et al. (1991) are perhaps not what they should be. In this study, the adverse effects were recorded by parents. Only 220 (treatment = 107, control = 113) out of a total of 232 (treatment = 114, control = 118) diaries were collected. Using the total group size in the numerator (also done in Burke at al. (1991)) is thus not appropriate.

Finally, it is not clear if the numbers for adverse effects in Burke et al. (1991) and Damoiseaux et al. (2000) included the cases known or suspected to have dropped out of the study due to an adverse effect.

In our view, this meta-analysis should be modified as follows: First, do not use the data on vomiting until it is reported in at least one other study. Second, do not use a composite adverse effect outcome. Instead, perform separate meta-analyses for diarrhoea and rash. Third, for Damoiseaux et al. (2000), use the total numbers for day 4 and day 11, with the above noted qualification in mind. Fourth, for Burke et al. (1991) change the denominators as noted above. Finally, include drop outs due to side effects in the meta-analyses. The table below gives the possible numerators to be used for these meta-analysis.

Separated Data on Side Effects

Vomiting Diarrhea Rash

Study T C T C T C

Thalin et al. (1985) ? ? 0 0 1 1

Burke et al. (1991)+ 20 14 24 16 16 9

Mygind et al. (1981) ? ? 2 1 1/2? 0

Damoiseaux et al. (2000)*,+ ? ? 20 12 0 3

Damoiseaux et al. (2000)? ? ? 34 22 0 3

Note: ? Unclear if vomiting not observed or not reported.

Note: ? = 2 if a dropout was not counted; else = 1.

* Day 4; ? Day 4 and Day 11; + unclear if dropouts counted.

2) Contralateral AOM

The occurrence of contralateral AOM, as is made clear in Glasziou et al. (2004), is relevant for only the cases with unilateral AOM at the outset. This numbers in the table below are used for the meta-analysis of this outcome in Glasziou et al. (2004).

Outcome: Contralateral AOM

Study Treatment Control

Thalin et al. (1985) 4/159 17/158

Burke et al. (1991) 29/98 33/102

Mygind et al. (1981) 2/72 6/77

Overall 35/329 56/337

The first problem is clinical heterogeneity, as noted in the table below. The issues in that respect are similar to those stated for the meta-analysis of adverse effect.

Clinical Heterogeneity: Contralateral AOM

Study Time Period Evaluator(s)

Thalin et al. (1985) day 8-10 or day 30 ENT Physician

Burke et al. (1991) 21 days Parent

Mygind et al. (1981) 1 week Physician

A further problem with this meta-analysis is the denominators used. Consider this issue for each study.

Thalin et al. (1985): The denominators in Glasziou et al. (2004) include unilateral and bilateral cases. Only 82% of the episodes were unilateral at the start but the breakdown by group is not given in the paper. We obtained adjusted denominators as follows. Treatment: 0.82?159 = 130; Control: 0.82?158 = 130. The bias now remains the same but the precision level is now corrected.

Burke et al. (1991): The denominators represent the total unilateral cases for each group. The study authors used these denominators. Completed 21-day diaries, the source of data on contralateral otitis, were, however, available only for 107 (of 114) in the treatment group and 113 (of 118) in the control group. So either one assumes that only the bilateral cases had missing diaries (which is unlikely) or that the rate of missingness in each group was not affected by laterality. In the latter case, the adjusted denominators are: Treatment: (98?107)/114 = 92; Control: (102?113)/118 = 98. The level of bias remains unknown but the precision level is possibly better.
Mygind et al. (1991): The denominators used include unilateral and bilateral cases. But there were 8 bilateral cases in the placebo group and 14 in the control group. So the appropriate denominators are Treatment: 72 - 8 = 64; Control: 77 - 14 = 65. The bias and precision levels are now corrected.
The appropriately adjusted data for this meta analysis are given below.
Contralateral AOM: Adjusted Data
Study Treatment Control
Thalin et al. (1985) 4/130 17/130
Burke et al. (1991) 29/92 33/98
Mygind et al. (1981) 2/64 6/65
Overall 35/286 56/294
References
1. Burke P, Bain J, Robinson D and Dunleavey J (1991) Acute red ear in children: Controlled trial of non-antibiotic treatment in general practice, British Medical Journal, 303, 558?562.
2. Damoiseaux RAMJ, van Balen FAM, Hoes AW, Verheij TJM and de Melker RA (2000) Primary care based randomised, double blind trial of amoxicillin versus placebo for acute otitis media in children aged under 2 years, British Medical Journal, 320: 330?334.
3. Glasziou PP, Del Mar CB, HayemMand Sanders SL (2004) Antibiotics for acute otitis media in children, Cochrane Database of Systematic Reviews, 2004; (1): CD000219. Art. No: CD000219, DOI: 10.1002/14651858.CD000219.pub2 (21pages)
4. Mygind N, Meistrup-Larsen K-I, Thomsen J, Thomsen VF, Josefsson K and Sorenson H (1981) Penicillin in acute otitis media: a double-blind placebo-controlled trial, Clinical Otolaryngology, 6: 5?13.
5. Thalin A, Densert O, Larsson A, Lyden E and Ripa T (1986) Is penicillin necessary in the treatment of acute otitis media? In: Proceedings of the International Conference on Acute and Secretory Otitis Media, Amsterdam, The Netherlands, Kegler Publications, pages 441?446.
Submitter agrees with default conflict of interest statement:
I certify that I have no affiliations with or involvement in any organization or entity with a financial interest in the subject matter of my feedback.

Reply

1) We acknowledge the variation in methods of collecting and recording information on adverse events and in the types of adverse events reported in the included trials. We contend however, that considering vomiting, diarrhoea or rash as an entity is justified by the easier interpretation it provides . Though the events are biologically very different, they are of similar seriousness; irritating and difficult to manage but minor in nature. Also, as pointed out in the above comments, dividing the adverse events into each type would not be helpful as they are infrequently reported (i.e. vomiting is only reported in one study). We recognise that 'lumping' the adverse events together is a crude approach but believe the benefits in continuing to do so outweigh the drawbacks. In the discussion section of this update we have made reference to the results of the individual patient data meta analysis (Rovers 2006) (which included a subset [n = 6] of the trials included in this review [n = 10]) which reports separately on the frequency of diarrhoea and rash in the treatment and control groups. We appreciate your consideration and suggestions related to the inclusion of drop outs due to side effects in the Burke and Damoiseaux studies. Corrections to the data have been incorporated.
2) Thankyou for pointing out the numerical errors in the meta analysis of contralateral AOM. We have corrected the analysis as suggested. This results in a minor changed to the pooled random effects OR (OR 0.44 95% CI 0.16, 1.26 versus 0.45 95% CI 0.16, 1.23) with antibiotics appearing to reduce contralateral AOM though the effect was not significant with the random effects model.

Contributors

Karim F. Hirji, D.Sc
Peter C. Gøtzsche

Antibiotics for acute otitis media in children, 8 March 2011

Summary

The title and conclusion of the review need revising as it is just reviewing the effect of penicillin family antibiotic on the AOM and not other antibiotics. It is suggesting to changed the title to "Usage of penicillin family Antibiotics for acute otitis media in children". Warm regards.
P.S: The only included trials were too old and they just used the publish data:
Halsted 1968 ampicillin 100 mg/kg/day or phenethicillin 30 mg/kg/day plus sulphisoxazole 150 mg/kg/day
Howie 1973 one of erythromycin, ampicillin, or triple sulphonamide plus erythromycin
Submitter agrees with default conflict of interest statement: I certify that I have no affiliations with or involvement in any organization or entity with a financial interest in the subject matter of my feedback.

Reply

The title is our intention. However, as you point out, it just so happens that most (but not all) antibiotics trialled against placebo for acute otitis media were from the penicillin group. Moreover more trials might be undertaken using non-penicillin antibiotics. So it is appropriate to retain the original title.
Chris Del Mar, 19 June, 2012

Contributors

Amirkambiz Hamedanizadeh, Medical Doctor

WHAT'S NEW

Last assessed as up-to-date: 8 November 2012.

Date	Event	Description
8 November 2012	New citation required but conclusions have not changed	The general conclusions and recommendations regarding the effectiveness of antibiotics on pain and adverse events remained unchanged. Antibiotic treatment lead to a statistically significant reduction of children with AOM experiencing pain at two to seven days compared with placebo, but since most children (82%) settle spontaneously, about 20 children must be treated to prevent one suffering from ear pain at two to three and four to seven days. (In the previous version the number needed to treat to benefit (NNTB) was 16). However, in this updated review antibiotic treatment appeared to have a statistically significant beneficial effect on the number of tympanic membrane perforations (risk ratio (RR) 0.37, 95% confidence interval (CI) 0.18 to 0.76; NNTB 33) and contralateral acute otitis media (AOM) episodes (RR 0.49, 95% CI 0.25 to 0.95, NNTB 11) as compared with placebo For every 14 children treated with antibiotics one child

(*Continued*)

		experienced an adverse event (such as vomiting, diarrhea or rash) that would not have been occurred if antibiotics were withheld. (In the previous version the number needed to treat to harm (NNTH) was 24) Antibiotics are most useful in children under two years of age with bilateral AOM, or with both AOM and otorrhoea. For most other children with mild disease, an expectant observational approach seems justified. We have no data on populations with higher risks of complications
8 November 2012	New search has been performed	A new review author joined the team to update this review. We updated the searches in November 2012. Two new trials were identified for the review of antibiotics against placebo (Hoberman 2011; Tähtinen 2011). These studies included children < 35 months of age and provided data on pain (Tähtinen 2011), contralateral otitis, late recurrences (Hoberman 2011), perforation and adverse events (Hoberman 2011, Tähtinen 2011) . The Laxdal 1970 trial has been removed from the review of antibiotics against placebo and added to the review of immediate antibiotics versus expectant observation No new trials were identified for the review of immediate antibiotics compared with expectant observation. Furthermore, we did not identify ongoing trials In this updated review, we now provide outcome data for pain at 24 hours, two to three days and four to seven days (in earlier versions outcome data for pain were presented at 24 hours and two to seven days)
19 June 2012	Feedback has been incorporated	Feedback added to review

HISTORY

Protocol first published: Issue 1, 1995

Review first published: Issue 3, 1996

Date	Event	Description
2 September 2009	Amended	95% confidence intervals for the outcome pain at 2-7 days and adverse events stated in the abstract and body of the review corrected

(*Continued*)

2 July 2008	New search has been performed	The search was updated in July 2008. Four new trials were identified and included in the review (Le Saux 2005, Spiro 2006, Neumark 2007 and McCormick 2005). One of these trials (Le Saux 2005) compared antibiotics with placebo. For the outcome pain at 24 hours and 2 to 7 days, inclusion of this trial did not alter the overall conclusions of the primary analysis. The three other new trials (Spiro 2006, Neumark 2007, McCormick 2005) compared immediate antibiotics with various observational approaches. One of the new trials compared immediate antibiotics with delayed prescribing (Spiro 2006). The other trials (McCormick 2005 and Neumark 2007) compared immediate antibiotics with 'watchful waiting', in which no prescription was supplied but advise on when to seek treatment was provided. Outcome data on pain at 3 to 7 days from these trials were analysed with data from another trial of immediate versus delayed prescription (Little 2001). In earlier versions of the review data from the Little (Little 2001) trial had been included in a sensitivity analysis. In this update, data from the four trials comparing immediate versus observational management strategies have been included in the main analysis. Information on subgroups of children who are most likely to benefit from treatment with antibiotics, obtained from a meta-analysis of individual patient data has been included in this review (Rovers 2006). Methods of the IPD meta-analysis, conducted by two authors on this review (and others) are also included. Survival curves from the IPD meta-analysis showing the pattern of recovery from acute otitis media over time has been included as an extra figure. Two ongoing trials comparing antibiotics with placebo in children < 35 months have been identified
17 January 2008	Amended	Converted to new review format.
4 September 2007	Feedback has been incorporated	Feedback added.
18 February 2005	Feedback has been incorporated	Feedback and reply added.
24 March 2003	New search has been performed	Searches conducted.
24 August 2002	Feedback has been incorporated	Feedback added.
17 February 2002	Feedback has been incorporated	Feedback added.
20 November 2000	Feedback has been incorporated	Feedback comments and replies added.

(*Continued*)

3 February 2000	New citation required and conclusions have changed	Conclusions changed.
3 February 2000	New search has been performed	Searches conducted.
30 December 1998	New search has been performed	Searches conducted.
30 July 1994	New search has been performed	Searches conducted.

CONTRIBUTIONS OF AUTHORS

Chris Del Mar (CDM) and Paul Glasziou (PG) prepared the original version of the review.

Sharon Sanders (SLS) conducted searches, identified studies, extracted data and prepared manuscript for the updated reviews in 2003, 2007 and 2008.

Maroeska Rovers (MMR) participated in the 2007 update by providing data and information from the individual patient data meta-analysis that has been included in this update.

Roderick Venekamp (RPV) conducted searches, identified studies, extracted data and prepared manuscript for the updated review in 2012.

PG, CDM, MMR, SLS and RPV have reviewed and provided comment on the updated version of the review.

DECLARATIONS OF INTEREST

None noted.

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; Age Factors; Anti-Bacterial Agents [adverse effects; *therapeutic use]; Earache [drug therapy]; Otitis Media [*drug therapy; prevention & control]; Randomized Controlled Trials as Topic; Recurrence [prevention & control]; Tympanic Membrane Perforation [drug therapy]

MeSH check words

Adolescent; Child; Child, Preschool; Humans; Infant